Temperature and barometric pressure were also measured. Individual subject data were analyzed separately by regression analysis. The coefficients were then tested using a non-parametric Wilcoxon signed rank test. None of the PM measures were associated with changes in any of the health endpoints. This study had very low power, given the small sample size and lack of high PM levels.

***Acute Pulmonary Function Studies Summary***

Pulmonary function results are slightly easier to compare because most studies used peak flow (PEFR) or forced expiratory volume (FEV) as the health end-point measure. The acute pulmonary function studies (summarized in Table 12-13) are suggestive of a short term effect resulting from PM pollution. Peak flow rates show decreases in the range of 30 to 40 ml/sec resulting from an increase of 50 µg/m$^3$ in $PM_{10}$ or its equivalent (see Figure 12-6). The results appear to be larger in symptomatic groups such as asthmatics. The effects are seen across a variety of study designs, authors, and analysis methodologies. Effects using $FEV_1$ or FVC as endpoints are less consistent. For comparison, a study of over 16,000 children found that maternal smoking decreased a child's FEV by 10 to 30 ml (Hasselblad et al., 1981).

Pope and Kanner (1993) provided one estimate of the effect of PM on pulmonary function in adults. They found a 29 (±10) ml decrease in $FEV_1$ per 50 $\mu$g/m$^3$ increase in $PM_{10}$, which is similar in magnitude to the changes found in children. Dusseldorp et al. (1994), in comparison, found 45 and 77 ml/sec decreases for evening and morning PEFR, respectively, per 50 $\mu$g/m$^3$ increase in $PM_{10}$.

## 12.4 HEALTH EFFECTS OF LONG-TERM EXPOSURE TO PARTICULATE MATTER

### 12.4.1 Mortality Effects of Long-Term Particulate Matter Exposures

The long-term effects of air pollution may be examined by considering gradual changes over time (the longitudinal study) or by contrasting spatial differences at a given point in time (the cross-sectional study). Longitudinal studies examine the effects of long-term changes in air quality, such as those that accompany pollution abatement campaigns. Only a

## TABLE 12-13 (cont'd). ACUTE PULMONARY FUNCTION CHANGES

| Study | PM Type & No. Sites | PM Mean & Range‡ | Model Type & Lag Structure | Other Pollutants Measured | Weather & Other Factors | Pollutants in Model | Decrease* (Confidence Interval) |
|---|---|---|---|---|---|---|---|
| Koenig et al. (1993), study of asthmatic and non-asthmatic elementary school children in Seattle, WA in 1989 and 1990 | $PM_{2.5}$ calibrated from light scattering | $PM_{2.5}$ ranged from 5 to 45 µg/$m^3$ | Random effects linear regression | none | height, temperature | $PM_{2.5}$ | Asthmatics<br>$FEV_1$ 42 ml (12, 73 ml)<br>FVC 45 ml (20, 70 ml)<br>Non-asthmatics<br>$FEV_1$ 4 ml (-7, 15 ml)<br>FVC -8 ml (-20, 3 ml) |
| Hoek and Brunekreef (1993), study of children aged 7 to 12 in Wageningen, Netherlands | Single site measure black smoke. $PM_{10}$ was measured during episodes | $PM_{10}$ range of 30 to 144 µg/$m^3$ | SAS procedure AUTOREG | $SO_2$, $NO_2$ | day of study | PM | $PEFR_{10}$<br>41 ml/s (-8, 90) |
| Roemer et al. (1993), study of children with chronic respiratory symptoms in The Netherlands | Single site measure black smoke. $PM_{10}$ was measured using an Anderson dichot | $PM_{10}$ range 30 to 144 µg/$m^3$ | multiple linear regression analysis | $SO_2$, $NO_2$ | none | $PM_{10}$ | PEFR<br>34 ml/s (9, 59) |
| Pope and Kanner (1993), study of adults in the Utah Valley from 1987 to 1989 | $PM_{10}$ was collected daily from the north Salt Lake site | $PM_{10}$ daily mean 55 µg/$m^3$, range 1 to 181 µg/$m^3$ | Linear regression on difference in PFT as a function of $PM_{10}$ | Limited monitoring of $SO_2$, $NO_2$, and ozone | low temperature | $PM_{2.5}$ | $FEV_1$ 29 ml (7, 51 ml)<br>FVC 15 ml (-15, 45 ml) |
| Neas et al. (1995), study of 83 children in Uniontown, PA, in the summer of 1990 | One site mean 2 km north of center of town; measured $PM_{2.5}$ and $PM_{10}$ | Mean $PM_{10}$ 36 $\mu$g/$m^3$ max. 83 $\mu$g/$m^3$<br>Mean $PM_{2.5}$ 25; max. 88 $\mu$g/$m^3$ | Autoregressive liner regression model | $O_3$, $SO_2$, sulfate, $H^+$ | Temperature | None | PEFR per 25 $\mu$g/m PM : 23.1 (-0.3 to 36.9 ml) |

## TABLE 12-13 (cont'd). ACUTE PULMONARY FUNCTION CHANGES

| Study | PM Type & No. Sites | PM Mean & Range‡ | Model Type & Lag Structure | Other pollutants measured | Weather & Other Factors | Pollutants in model | Decrease* (Confidence Interval) |
|---|---|---|---|---|---|---|---|
| Studnicka et al. (1995), study of 133 children at a summer camp in southern Austria in 1991 | One site located at the camp measured $PM_{10}$ | Means by time period ranged from 6.6 to 10.7 $\mu g/m^3$ | Linear regresison with repeated measures | $H^+$, $SO_2$, ammonia | Temperature, humidity, pollen, gender, height, age | $H^+$ | FVC 17.5 ml (-64.0, 99.0)<br>$FEV_1$ 66.5 ml (-10.0, 143.0)<br>PEFR 99 ml/s |
| Hoek and Brunekreef (1994), study of children in 4 towns in The Netherlands | No. of sites not given 24-h $PM_{10}$ measured | Mean $PM_{10}$ 45 $\mu g/m^3$, range 14-126 $\mu g/m^3$ | Box-Jenkins first order autoregressive model | $SO_2$, $NO_2$, sulfate, nitrate, HONO | Minimum temperature | None | FVC -0.5 ml (-3.5, 2.5); $FEV_1$ 5.0 ml (-1.0, 11.0)<br>PEFR 41.0 ml/sec (12.5, 69.5) |
| Dusseldorp et al. (1994), study of 32 adults in a steel plant in Wijkaan Zee, The Netherlands | $PM_{10}$ measured at 3 sites | $PM_{10}$ mean 54 $\mu g/m^3$, range 4-137 $\mu g/m^3$ | Multiple linear regression with first order autocorrelation | Iron, Mn, sodium, silicon | Wind direction, temperature | Iron | PEFR evening 45 ml/sec (9, 81)<br>PEFR morning 77 ml/sec (34, 119) |

*Decreases in lung function calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in $PM_{10}$ or 100 $\mu g/m^3$ increase in TSP.
‡Means and Ranges listed if reported by authors.

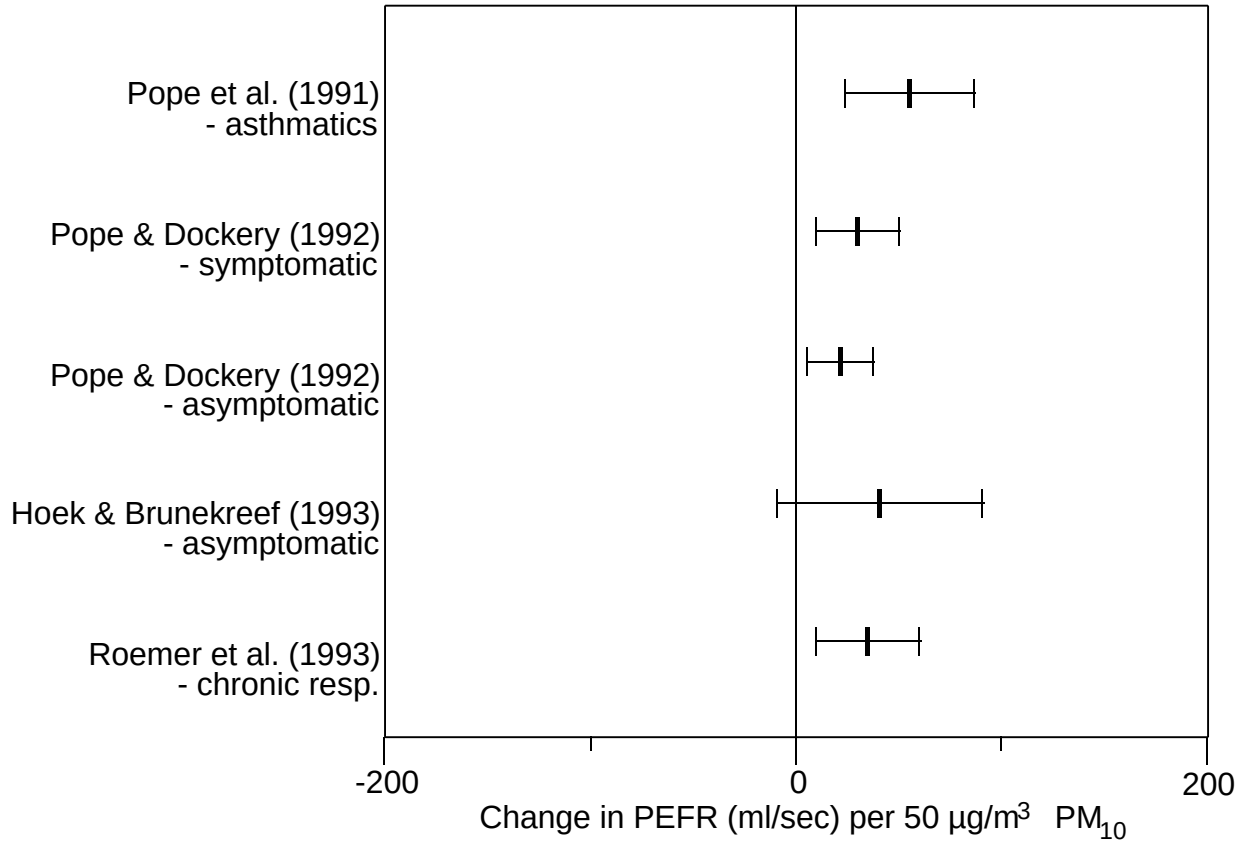


**Figure 12-6. Selected acute pulmonary function change studies showing change in peak expiratory flow rate (ml/s) per 50 $\mu$g/m$^3$ $PM_{10}$ increases.**

few such studies have been published (Lipfert, 1994a); none recently. Cross-sectional studies are designed to infer the accumulated long-term effects of the environment by contrasting spatial differences. As with all epidemiology, such spatial gradients may only be credibly attributed to air quality after the potential confounders have been controlled.

Mortality rates or probabilities of survival may differ by location for any of a number of reasons. Long-term health risk factors may be further subdivided into factors that relate to the population of a given place (age, race, education, lifestyle, for example) and factors that relate to the physico-chemical environment of that place (climate, air and water quality). There are also likely to be interactions between these two subcategories, since places with desirable environments may attract as in-migrants that portion of the population that is better off

economically while the disadvantaged part of the population may be forced to remain in less desirable locations and in those with depressed economies.

Annual mortality rates must also reflect the net sum of acute events that took place that year (Evans et al., 1984a). If the increases in daily death rates associated with acute events are not subsequently canceled by decreases (a phenomenon referred to as "harvesting"), annual rates will indicate the history of these acute effects. Thus, differences in long-term mortality rates associated with air pollution are likely to reflect some combination of acute and chronic effects. Although both types of information are useful contributions to the overall understanding of the health effects of air pollution, their distinction may be difficult if based on statistical criteria alone.

Long-term mortality studies are considered here in two groups:

1. Cross-sectional studies based entirely on the characteristics of groups averaged across various geopolitical units, referred to as population-based studies.

2. Prospective cohort studies based on (a) health and demographic data for individuals and (b) air pollution exposure data were based on community-wide averages in much the same way as the population-based studies.

None of the studies available for review had individual data on personal exposures to air pollution. The population-based studies used annual mortality rates and annual average air quality data, usually for coincident periods centered on decennial census years. Brief considerations have been given to exposures lagged by 10 or more years in several instances, in an attempt to deduce effects of exposures over longer periods. The prospective studies consider the net survival rates over a multi- year period of follow-up; various assumptions were made by the different investigators about the appropriate timing of air pollution exposures. The studies thus varied in terms of their ability to provide either a measure of lagged chronic effects or an integrated measure of acute effects during a given period.

#### 12.4.1.1 Methodological Considerations

Methods for cross-sectional analysis were considered in a general way in the Methodology discussion (Section 12.2). However, there are some specific guidelines that should be considered with respect to the estimation of long-term effects on the basis of spatial gradients. In general, the most difficult problems are (1) collinearity among pollutants, (2) variable and inadequate characterizations of pollutant exposure, and (3) confounding by non-pollutant variables.

However, these issues are somewhat different than those encountered in the acute mortality and morbidity studies. Collinearity between PM and some pollutants may be less of a problem because of differences among regions in typical pollution sources, with sulfur oxides a relatively more important factor in eastern communities and nitrogen oxides relatively more important in western communities. On the other hand, with multiple years of pollutant data collected on a daily or every-sixth-day schedule, it may be possible to construct a variety of different pollution exposure indices from the same data base, with different indices more or less correlated in any analysis. The second concern is that of adequately characterizing long-term exposures, with choices of long-term averages, current year averages, or moving averages lagged by years rather than days, seasonal weights, etc. The third problem, confounding by other factors, now includes demographic differences among communities that may affect baseline mortality rates, and also change over time.

The study of long-term or chronic health effects of air pollution began with population-based studies and became fraught with difficulty and controversy, more so than the short-term studies (Smith, 1975; Lipfert, 1980a; Ware et al., 1981; Ricci and Wyzga, 1983; Evans et al., 1984b). The primary method of analysis involves comparing the health statistics of populations of places which have had different environments over the long-term. However, the comparisons are often complicated or even compromised by other differences that may be related to the sources and effects of air pollution, such as industrialization or climate. Cross-sectional studies often use data from only one specific year that may or may not be truly representative of long-term environmental conditions.

The most recent contributions to this literature have involved prospective survival analysis of defined cohorts. These studies offer the potential of much more credible results because of their ability to draw upon individual characteristics such as smoking status. Stratification

effectively reduces any uncertainties as to whether a potential confounder has been adequately controlled.

***Example of Spatial Confounding***

Some air pollution indices such as sulfates appear to have substantial potential for confounding, because they are collinear with several important socioeconomic indicator variables that relate to the geographic concentration of both the air pollutant and the covariate in various parts of the country. For example, regression analysis of 1980 SMSA data (Lipfert, 1992) has shown that the migration variable, defined here as the percentage change in SMSA population from 1970 to 1980, is one of the most important potential confounders for sulfate. When migration is included in a regression for all-cause or cardiovascular mortality, neither $SO_4^{2-}$ nor immigration are statistically significant predictors. Thus, separating the effects of these two collinear variables is critical in estimating the mortality response to sulfates or other air pollutants.

Additional reanalyses of data reported on by Lipfert (1992) for this document further evaluated impacts of migration as a potential confounders in long-term PM exposure studies. The 149 SMSAs were trichotomized by migration tertiles: SMSAs with less than 4.5% population gain, SMSAs with gains from 4.5 to 15%, and SMSAs with more than 15% gain. Cross tabulations showed the following variables be monotonic across these divisions:

- variables that increased with population gain (% black, % poor, % with college education, % other nonwhite, annual average Pb concentration);

- variables that decreased with population gain (mortality rates for all causes and for major cardiovascular causes, degree days, median age, % over 65, concentrations of $SO_2$, $SO_4^{2-}$, $NO_x$, $PM_{2.5}$, Mn).

This suggests that the migration variable might act as a delineator between northern "rustbelt" locations with shrinking economies and southern and "sunbelt" locations with growing economies. Studies on individuals have shown that selective migration can have an effect on the health status of a community, which is what is being analyzed in a population-based study. As noted previously, other sociodemographic variables can also be confounded with location, such as the correlation of high percentages of Hispanic residents with high TSP concentrations in the southwestern states.

Regression analyses involving these variables showed the following:

(a) Substituting the trichotomized migration variable for the continuous measure of population change shifted the mortality response from population change to sulfate: the OLS coefficient increased from 0.028 (s.e. = 0.016) to 0.045 (s.e. = 0.016). This is an example of how an incomplete specification for a confounder can increase the apparent response for the "confoundee" without inflating its standard error (the classic symptom of collinearity).

(b) Stratifying by the 3 levels of migration showed that the continuous population change variable remained significant in all 3 levels, while $SO_4^{2-}$ was only significant in the two strata with smaller population gains. Stratifying by $SO_4^{2-}$ (two levels) showed that $SO_4^{2-}$ was a significant (positive) predictor of mortality only in the higher stratum (with or without the population change variable), while population change was consistently significant in both strata.

Figure 12-7 extends this analysis to $PM_{2.5}$, for a smaller number of locations. Here the slope reduction due to introducing additional nonpollution variables is less dramatic but still notable. Figure 12-7a shows the regression model for 62 SMSAs when only age and race are used as covariates; here, a strong positive relationship between $PM_{2.5}$ age- and race-adjusted mortality is evident. When mortality is also adjusted for smoking , education, overweight, ethnicity, water hardness, sedentary lifestyle, poverty, and migration (Figure 12-7b,) the strength of the relationship with $PM_{2.5}$ decreases (but is not eliminated) and residual variability is significantly reduced. Thus, confounding by covariates such as migration merely reduced the effect size estimate for fine particles, but markedly diminished the relationship between sulfates and mortality.

***Spatial Patterns in the United States***

Spatial patterns of U.S. mortality rates show some well-defined trends that have existed for decades (Lipfert, 1994a). Such patterns are sometimes called the "geography of disease." In general, heart disease is higher east of the Mississippi and ischemic heart disease shows even sharper gradients and peaks in the Northeast (part of this gradient could be due to differences in diagnostic practices, although cold weather has also been implicated. Pneumonia and influenza deaths are generally well distributed across the country but tend to be higher north of about the

36th parallel. In contrast, the "stroke belt" has been defined as a broad east-west stripe across the southern part of the United States.

Spatial trends in air pollution have both local and regional patterns. Local patterns within cities reflect the presence of primary pollutants from local sources (CO from traffic, particles from industrial operations, $SO_2$ and $NO_2$ from combustion sources, for example).

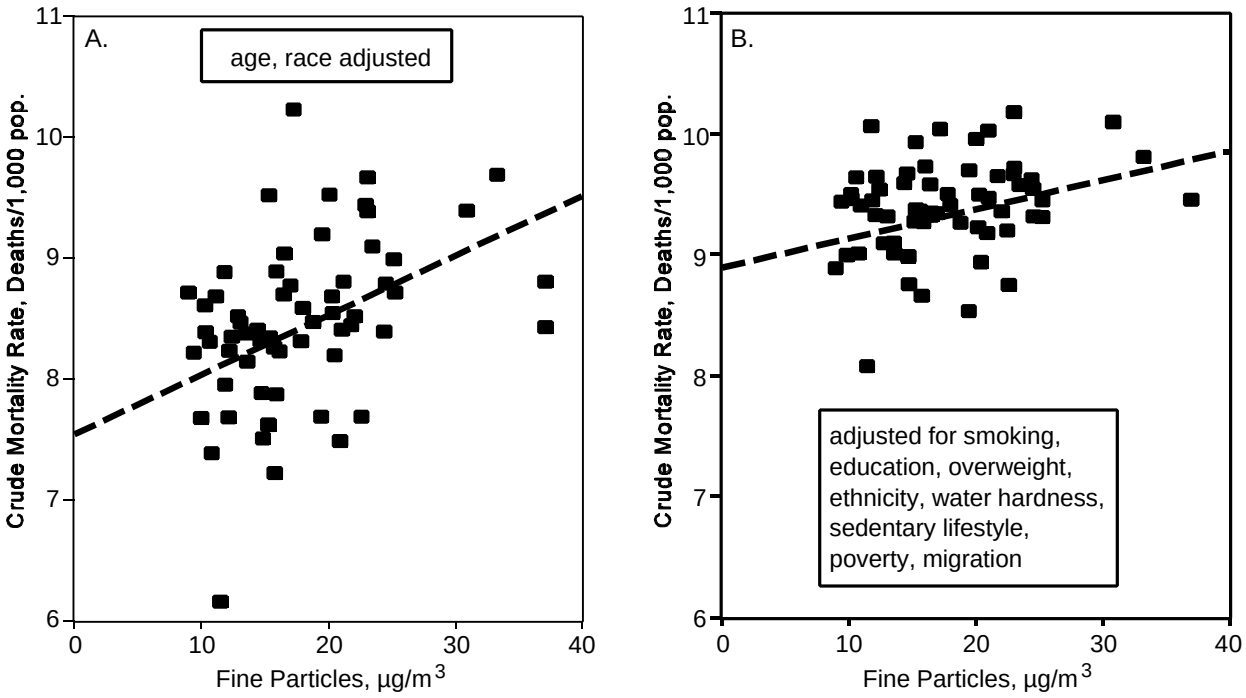


**Figure 12-7. Effect of confounding on $PM_{2.5}$-mortality relationship in 1980 SMSA data. The $PM_{2.5}$ effect on mortality is reduced (but not eliminated) by the introduction of numerous potentially confounding variables (e.g., smoking, migration, etc.) into regression analyses as shown in Panel B in comparison to analyses only including age and race adjustments illustrated in Panel A.**

Source: U.S. EPA reanalysis of data reported by Lipfert (1992).

There are also multi-state regional patterns in secondary pollutants, such as sulfates and other fine particles in Appalachia and the east north central "rust belt," and ozone in Southern California and along the Northeast corridor from Washington to Boston. Collinearity among pollutants results from common spatial patterns of their major sources.

The possibilities for confounding by regional factors vary with the scale of the analysis; comparisons within regions may thus be less susceptible than comparisons across the whole country. For this reason, consistency between different types of studies becomes very important in considering causality.

***Risk Measures***

Most of these studies consider deaths from all causes. Some of them subtract deaths due to accidents, homicides, and suicides, yielding a quantity referred to by various authors as "nonexternal" deaths, "deaths from all natural causes," or "all-disease deaths." Measures of the risks attributed to air pollution differ by type of study and regression model. Some studies report relative risks (mortality ratios) associated with specified but arbitrary pollution "reference" levels, such as 100 $\mu g/m^3$ of particulate matter or 50 ppb of ozone. These figures are obtained by multiplying the regression coefficient (the relative risk per unit of pollution) times the desired pollution level. This practice is convenient for comparing studies of the same pollutant but is less suitable for comparing the relative effects of different pollutants, because the actual relationship between pollutants in a given city may not correspond with that assumed by the reference levels. Others report ordinary least-squares regression coefficients in the original units of the study, such as change in annual death rate per unit of pollution. These coefficients are specific to the measures used for both dependent and independent variables, but may be converted to approximate log-linear coefficients or relative risk by dividing by the mean value of the dependent variable.

One measure that is free of measurement units is the "elasticity," a term taken from economics defining a nondimensional regression coefficient of y on $x_i$ (at the mean) as

$$e_i = b_i \, x_i/\overline{y} \qquad (12.4.1\text{-}1)$$

Elasticities may be expressed as decimals or in percent and offer another measure of attributable risk, based on the mean values of the $x_i$. An elasticity of 0.04 thus corresponds to a relative risk of 1.04 at the mean pollution level. Comparison of two elasticities may be misleading if the mean values differ widely. Note that when the "effect" of a variable ($b_i x_i$) is expressed as a percentage of the mean total response, "effect" and elasticity are synonymous.

***Model Specifications for Long-term Mortality Studies***

Because of the large number of potential confounding variables in spatial analysis, multiple regression has been the statistical method of choice. Some epidemiological studies have included the effects of both air quality and drinking water quality (mainly water hardness; see Pocock et al., 1980, for example). Models for population studies may be either linear or log-linear, and some investigators have included pollutant thresholds using piecewise linear models. For population-based studies, the dependent variable is usually an annual mortality rate for the geographic unit in question. It can be argued that, if age adjustment is used for the dependent variable, it must also be used for any independent variable that may also exhibit age dependency (such as smoking or air pollution exposure) but this has generally not been done.

Prospective studies of individuals have featured the proportional hazards model, in which the risk factors are multiplicative (these coefficients correspond to elasticities). The dependent variable is thus dichotomous (alive or dead). The range in survival probability among adult individuals is quite large, encompassing more than two orders of magnitude in mortality rate, as a function of age and other individual risk factors. Years of medical research have identified some of these risk factors as genetic predisposition, exposure to infectious diseases, access to medical care, and personal lifestyles (including diet, exercise, and smoking habits).

In contrast, the variability among cities and Standard Metropolitan Statistical Area (SMSA) mortality rates is relatively modest, with a coefficient of variation (CV) of about 17% (Lipfert, 1993), most of which is due to differences in age distributions. This corresponds to a standard deviation in average longevity of only about 21 mo. This reduction in variability occurs because areas as large as SMSAs in the United States tend to be similar in terms of their average characteristics, especially within regions; i.e., most of the variability among individuals is "averaged out" by working with city-wide averages. It is thus much easier to accurately predict the death rate when it is averaged over some geopolitical unit than it is to predict the survival of an individual within some specified time period. In any case, the ability to accurately predict the effects of exposure to air pollution depends on the validity of the model. Unfortunately, it is unavoidable that all such models are incomplete and thus may contain the potential for bias (Cohen, 1994).

As discussed above in Section 12.2, in order to confound, a variable must be correlated with both the dependent variable and the independent variable of interest. This limits consideration of confounders to established mortality risk factors that are correlated with air pollution. However, this correlation need not be direct (i.e., associated with air pollution sources per se), but, for cross-sectional analysis, the correlation is more likely to arise due to common spatial patterns, for whatever reason. Thus, sulfate is (spatially) correlated with old age, since both are most common in the Northeast and Midwest "rustbelt" area, and TSP is correlated with the presence of Hispanics, since both these factors are generally high in the Southwest. In many cases, appropriate data on confounders are not available and surrogates must be used for the actual mortality risk factors. Education is an example; staying in school longer per se does not prolong life, but better educated individuals are likely to have higher incomes and thus access to better medical care; they may also have healthier personal lifestyles. Greenland and Robins (1994a) point out, with examples, that control of potential confounders "crucially hinges on adequate measurement of the potential confounders." Klepper et al. (1993) provide other examples.

Adequately controlling for identified likely confounders is not always as straightforward as it might appear. For example, the relationship between education and health is likely to be nonlinear, as is the relationship between income and longevity (Rogot et al., 1992). Alcohol consumption and body mass are two of the risk factors that have also been shown to have non-linear relationships with mortality (see Grønbæk et al., 1994, for example). It therefore follows that the assumption of linearity may not be always be appropriate for surrogate risk factors.

State-level survey data on many other behavioral risk factors have recently become available (Siegel et al., 1993), and many of these factors are also correlated with sulfate concentrations. For example, the state-level correlation with "% 65 and over with sedentary life-style" was 0.64. The spatial collinearity between sulfate and these demographic/lifestyle factors is similar to that between daily air pollution and weather and presents a challenge to the analyst to separate cause from circumstance.

In some cases, ambient air quality monitors are sited near the locations of the worst air quality, near point sources or in the densest part of a city, in keeping with their intended regulatory function. Thus, they may overestimate the exposures of persons living in more distant

suburban areas. This is most likely to be the case for primary pollutants, such as CO, $NO_2$, $SO_2$, and $PM_{10}$ (or TSP). The opposite may be true for some ozone monitors, because of the tendency for levels to be reduced near sources of NO. Secondary sulfate and other fine particles tend to have much longer lifetimes and thus to be more uniformly distributed over entire states or regions. Different relationships between ambient pollutant concentrations and personal exposure for different pollutants must also be considered (Chapter 7). Note that such differences in the reliability of exposure estimates will tend to bias the regression coefficients, giving an advantage to those pollutants with smoother distributions (Lipfert and Wyzga, 1995a). Because the socioeconomic characteristics of the population and, thus, their mortality risk factors are also nonrandomly distributed, especially at the local level within an SMSA, collinearity may result between their actual population exposures and these other mortality risk factors. More simply put, persons employed by a local pollution source may tend to live closer to that source, and it may thus be difficult to distinguish between their ambient exposures, their occupational exposures, and the personal characteristics that led to their employment and residence there.

Cross-sectional studies should therefore include adjustments or statisitical control of probable confounders, yet avoid overcontrol by not including variables that have only coincidental associations with no substantive basis.

#### 12.4.1.2 Population-Based Cross-Sectional Mortality Studies

In this section, recent cross-sectional studies not reviewed in earlier documents are discussed employing averages across various geopolitical units (cities, SMSAs, etc.). No data on individuals are used; the community- based study seeks to define the (average) community characteristics that are associated with its overall average health status, in this case annual mortality rate.

Studies published after 1985 are emphasized here, but it is also useful to refer to some of the earlier influential studies for context. Table 12-14 summarizes some of the findings

## TABLE 12-14. COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1960 to 1974 MORTALITY)

| Source | Health Outcome | Time Period/ No. Units | PM Indicators | PM Mean ($\mu g/m^3$) | PM Range/ (Std. Dev.) | Sites Per City | Mean City Pop. | Model Type | PM Lag Structure | Other Pollutants | Other Factors | Relative Risk[1] at TSP = 100, $SO_4$ = 15 | RR. Confidence Interval | Elasticity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lave and Seskin (1977) Regr. 3.3-1 | Total mortality | 1960, 117 SMSA, USA | TSP, min $SO_4$ | 118<br>4.7 | (41)<br>(3.1) | 1 | 447,000 [2] | OLS, joint | none | none | Pct. Age 65; Pct. nonwhite; Pop. density; Pct. poor pop. | 1.050 TSP<br>1.104 $SO_4$ | (1.01-1.09)<br>(1.03-1.18) | 0.059<br>0.033 |
| Lave and Seskin (1977) Regr. 5.2.2 | Total mortality | 1960, 117 SMSA, USA | TSP min $SO_4$ | 118<br>4.7 | (41)<br>(3/1) | 1 | 447,000 [2] | OLS, joint | none | none | Pct. Age 65; Pct. nonwhite; Pop. density; Pct. poor pop.; Home heating fuel | 1.019 TSP<br>1.030 $SO_4$ | (0.98-1.05)<br>(0.97-1.09) | 0.022<br>0.01 |
| Lave and Seskin (1977) Regr. 7.1-4 | Total mortality | 1960, 112 SMSA, USA | TSP min $SO_4$ | 95<br>3.5 | (29)<br>(1.9) | 1 | 570,000 [2] | OLS joint | none | none | Pct. Age 65; Pct. nonwhite; Pop. density, Pct. poor pop. | 1.091 TSP<br>1.129 $SO_4$ | (1.04-1.14)<br>(1.01-1.25) | 10.087<br>0.030 |
| Lipfert (1984) Regr. 4.2 | Total mortality | 1970, 111 SMSA, USA | TSP $SO_4$ | 96<br>10.9 | (29)<br>(4.5) | 1 | 989,000 | OLS, joint | none | none | Pct. Age 65; Pct. Afr. Amer.; Pct. other nonwhite; Pop. density; Pct. poor pop; adj. cig. sales, coal, wood, homeheat | 1.044 TSP<br>1.057 $SO_4$ | (0.98-1.07)<br>(1.01-1.11) | 0.034<br>0.042 |
| Lipfert (1984) Regr. 4.7 | Total mortality | 1970, 69 SMSA, USA | TSP $SO_4$ | 96<br>10.9 | (29)<br>(4.5) | 1 | 989,000 | OLS, joint | none | $O_3$ | Same as above, with water quality, without pop. adj. | 1.052 TSP<br>1.035 $SO_4$ | (0.99-1.12)<br>(0.98-1.09) | 0.054<br>0.026 |
| Lipfert (1984) Tbl. 6, Line 10 | Total mortality | 1970, 69 SMSA | non-S TSP, $SO_4$ | 80.5<br>11.0 | (25)<br>(4.4) | 1 | 989,000 | OLS, joint | none | $O_3$ | Pct. Age 65; Pct. Afr. Amer.; Pct. other nonwhite; Pop. density; Pct. poor; Pop. migration; adj. for adj. cig. sales, coal, wood, home heating, drinking water, | 1.074<br>1.019 | (1.00-1.14)<br>NS | 0.05<br>0.014 |

## TABLE 12-14 (cont'd). COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1960 to 1974 MORTALITY)

| Source | Health Outcome | Time Period/ No. Units | PM Indicators | PM Mean ($\mu g/m^3$) | PM Range/ (Std. Dev.) | Sites Per City | Mean City Pop. | Model Type | PM Lag Structure | Other Pollutants | Other Factors | Relative Risk at TSP = 100, $SO_4$ = 15 | RR. Confidence Interval | Elasticity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chappie and Lave (1982) Regr. 2-6 | Mortality from natural causes | 1974, 104 SMSA | TSP<br>$SO_4$ | 75<br>9.6 | (41)<br>(3.8) | 1 | 527,000 [2] | OLS, joint[3] | none | $SO_4$ [3] | Pct. Age 65; Pct. nonwhite; pop. density; income; | 0.99 TSP<br>1.23 $SO_4$ | NA<br>NA | -0.01<br>0.15 |
| Chappie and Lave (1982) Regr. 3-6 | Mortality from natural causes | 1974, 102 SMSA | TSP<br>$SO_4$ | 75<br>9.6 | (41)<br>(3.8) | 1 | 527,000 [2] | OLS, joint[3] | none | $SO_4$ [3] | Pct. Age 65; Pct. nonwhite; pop. density; income; tobacco sales, alcohol sales; pct. college grads; industries | 0.985 TSP<br>1.18 $SO_4$ | NA<br>NA | -0.015<br>0.12 |

[1]At TSP = 100 $\mu g/m^3$, $SO_4$ = 15 $\mu g/m^3$, concentration adjusted for migration.
[2]Median value.
[3]Regression used minimum, maximum, and mean values for TSP and $SO_4$ in the same model; relative risks were calculated from combined elasticity for each pollutant.

from these "background" studies, which analyzed mortality from 1960 to 1974. Studies that analyzed spatial variability in 1980 mortality are summarized in Table 12-15. Many of these studies comprise a large numbers of individual regressions; the tables indicate which ones were selected for discussion here, but the numerical column headings are more convenient for the discussion that follows.

***Background and Critiques of Some Older Studies***

Although there had been a few earlier intracity cross-sectional studies (Lipfert, 1994a), the current "model" for the cross-sectional population-based study was introduced by Lave and Seskin (1970, 1977). They published an extensive national cross-sectional regression analysis and concluded that about 9% of annual U.S. metropolitan mortality (ca. 1960) was associated with air pollution, considering TSP and $SO_4^{2-}$ jointly. The analysis was based on multiple linear regression analysis of annual mortality rates in the major SMSAs in relation to coincident annual air quality levels (as measured at city centers) and to selected other explanatory variables, listed in Table 12-14. This study was the first to attempt to characterize the air pollution exposure of an entire SMSA using (often fragmentary) data from a single monitoring station. Studies by several investigators showed that the annual mean was the preferred pollution metric. As shown in the first two studies in Table 12-14, introduction of a home-heating fuel variable resulted in loss of significance and reduced relative risks for both pollution variables. There are other examples of this type of instability in Lave and Seskin (1977).

Lipfert (1984) reanalyzed Lave and Seskin's 1969 total mortality data set for 112 SMSAs (third study in Table 12-14), using corrected data and many new independent variables, including 1970 mortality to correspond better with the socioeconomic variables obtained from the 1970 Census (fourth through sixth studies in Table 12-14). The analysis was incapable of distinguishing between linear and threshold models and thus could not rule out the applicability of a threshold or piecewise linear model. A threshold for TSP was suggested at about 85 to 130 $\mu g/m^3$, and for sulfate at about 10 to 15 $\mu g/m^3$.

## TABLE 12-15. COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1980 MORTALITY)

| Source | Health Outcome | Time Period/ No. Units | PM Indicators | PM Mean ($\mu g/m^3$) | PM Range/ (Std. Dev.) | Sites Per City | Mean City Pop. | Model Type | PM Lag Structure | Other Pollutants | Other Factors | Relative Risk[2] at TSP = 100, $SO_4$ = 15 | RR. Confidence Interval | Elasticity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Özkaynak and Thurston (1987) Table VI | Total mortality | 1980 98 SMSA | TSP | 78 | (26) | 1 | NA | OLS sep. | none | none | Pct. age 65; median age; | 1.012 TSP | (0.96, 1.06) | 0.01 |
| | | | $SO_4$ | 11.1 | (3.4) | | | | | | Pct. nonwhite; pop. density; Pct. poor, pct. w/ 4 yrs college. | 1.17 $SO_4$ | (1.09, 1.24) | 0.086 |
| Özkaynak and Thurston (1987) Table VII | Total mortality | 1980, 38 SMSA | $PM_{15}$ | 38 | (7.3) | 1 | NA | OLS sep. | none | none | Same as above. | 1.059 PM | (0.95, 1.16) | 0.045 |
| | | | $PM_{2.5}$ | 20 | (3.8) | | | | | | | 1.085 $PM_{2.5}$ | (0.96, 1.21) | 0.068 |
| Lipfert et al. (1988) Table 24 | Total mortality | 1980 172-185 cities | Fe, | 1.2 | (0.61) | 1 | 57,500 | OLS sep. | none | none | Pct. Age 65; birth rate; | 1.044 Fe | (1.02-1.07) | 0.041 |
| | | | $SO_4$ | 9.5 | (3.5) | | | | | | Pct. Afr.-Amer; pop. density, pct. poor; Pct. pop. change; pct. w/ 4 yrs. college; Pct. Hispanic; adj. cig., sales; Pct. prior res., hard water | 1.13 $SO_4$ | (1.06-1.20) | 0.071 |
| Lipfert et al. (1988) Table 24 | Total mortality | 1980 68 cities | $PM_{15}$ | 38 | (121) | 1 | 57,500 | OLS sep. | none | none | Same as above. | 1.036 PM | NS[3] | 0.027 |
| | | | $PM_{2.5}$ | 18 | (6) | | | | | | | 1.082 $PM_{2.5}$ | NS[3] | 0.059 |
| Lipfert et al. (1988) Page 60 | Total mortality | 1980 122 cities | TSP | 88 | (29) | 1 | about 60,000 | OLS joint | 10 years | none | Pct. age 65; birth rate; pct. nonwhite; pop. density; pct. poor; adj. cig. sales; pct. w/ 4 yrs. college. | about 1.0 | NS[3] | NS |
| | | | $SO_4$ | 9.0 | (1.8) | | | | | | | 1.072 $SO_4$ | (1.0, 1.14) | 0.037 |

## TABLE 12-15 (cont'd). COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1980 MORTALITY)

| Source | Health Outcome | Time Period/ No. Units | PM Indicators | PM Mean ($\mu g/m^3$) | PM Range/ (Std. Dev.) | Sites Per City | Mean City Pop. | Model Type | PM Lag Structure | Other Pollutants | Other Factors | Relative Risk[1] at TSP = 100, $SO_4$ = 15 | RR. Confidence Interval | Elasticity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lipfert (1993) Regr. 6.1, 6.2 | Mortality from natural causes | 1980 149 SMSA | TSP | 68 | (17) | 10.6 (TSP) | 928,000 | OLS sep. | none | none | Pct. age 65; Pct. Afr.-Amer.; Pct. Hispanic; Pct. other nonwhite; pct. poor; pop. density; pct. pop. change; adj. cig. sales; pct. w/ 4 yrs. college; hard water, heating degr. days. | 1.038 TSP | (0.97, 1.10) | 0.026 |
| | | | $SO_4$ | 9.3 | (3.1) | | | | | | | 1.059 $SO_4$ | (0.99, 1.12) | 0.037 |
| Lipfert (1993) Regr. 13.1, 13.3 | Mortality from natural causes | 1980 62 SMSA | $PM_{15}$ | 38 | (29) | 1 | 928,000 | OLS sep. | none | none | Same as above | 1.036 PM | (0.98, 1.10) | 0.027 |
| | | | $PM_{2.5}$ | 18 | (4.5) | | | | | | | 1.060 $PM_{2.5}$ | (0.99, 1.13) | 0.043 |
| Lipfert (1993) Regr. 9.1, 9.3 | Mortality from natural causes | 1980 62 SMSA | TSP | 68 | (17) | 10.6 (TSP) | 928,000 | Log-linear | none | none | Same as above without other nonwhite, heating degr. days, pop. density | 1.066 TSP | (1.006, 1.13) | 0.044 |
| | | | $SO_4$ | 9.3 | (3.1) | | | | | | | 1.021 $SO_4$ | NS | 0.012 |
| Lipfert (1993) Regr. 13.5 | Major CVD | 1980 62 SMSA | $SO_4$ (IP) | 4.3 | (2.5) | 1 | 928,000 | OLS | none | none | Same as above with other nonwhite, heating degree days, pop. density | 1.04 $SO_4$ | NS | 0.011 |
| Lipfert (1993) Regr. 12.1 | Major CVD | 1980 62 SMSA | $SO_4$ (IP) | 4.3 | (2.5) | 1 | 928,000 | OLS | none | none | Pct. age 65; median age; pct. nonwhite; pop. density; pct., poor; pct. w/ 4 yrs coll. | 1.19 $SO_4$ | (1.03, 1.35) | 0.054 |
| Lipfert (1993) Regr. 10.3, 10.4 | COPD | 1980 149 SMSA | TSP-$SO_4$ | 56.4 | (18) | 10.6 | 928,000 | Log-linear | none | none | Pct. age 65; pct. Afr.-Amer.; Pct. Hispanic; pop. density; pct. poor; adj. cig. sales. | 1.50 TSP | (1.22, 1.83) | 0.23 |
| | | | TSP | 68.5 | (17) | | | | | | | 1.43 TSP | (1.20, 1.71) | 0.25 |

[1]All regression models used PM indicators one at a time (separate models) except as noted.
[2]At TSP = 100 $\mu g/m^3$, $SO_4$ = 15 $\mu g/m^3$, corrected for migration.
[3]NS = not statistically significant, confidence limits not available.

At this point in the development of the methodology for population-based cross-sectional studies (which was discussed in the 1982 CD and the 1986 Addendum [U.S. Environmental Protection Agency, 1982a, 1986a]), it appeared that the findings of national cross-sectional analyses (Table 12-14) showed that including additional socioeconomic variables in the model reduced the apparent effects of sulfate for the 1970 time period. However, the 1974 study found even larger effects of sulfate, but it could not be ascertained whether this was due to the regression model used or to the particular data set considered.

Kim (1985) analyzed total mortality data for 1970 in a cross-sectional analysis of 49 U.S. cities. Pollutants considered were TSP and the benzene-soluble organic fraction of TSP (BSO), in 5 different formats: averaged over the single years 1968, 1969, and 1970; averaged for 1969 to 1970, and for 1968 to 1970. This analysis was intended to test for lagged effects, but one might also expect the multiple-year averages to be superior because of the reduction of random sampling errors. Kim's lag analysis was largely inconclusive. He concluded "the effects of total mortality in 1970 may be due to the air pollution in 1969, although it is not possible to pinpoint a lag-effect between the time of exposure to air pollution and the time of death."

More recently conducted cross-sectional and/or prospective cohort studies address many of the concerns noted for the above-reviewed older studies.

***Studies of 1980 SMSA Mortality***

Ozkaynak and Thurston (1987) analyzed 1980 total mortality in 98 SMSAs, using data on $PM_{15}$ and $PM_{2.5}$ from the EPA inhalable particle (IP) monitoring network for 38 of these locations. The sulfate data from this network were not used in this study. The independent variables used are given in Table 12-15 (first two studies); in general, the regression modeling approach was similar to that of Lave and Seskin (1970). The results presented in Table 12-15 are from their "basic" regression model. Additional variables were explored, including spatial correlation variables intended to examine regionality and latitude and longitude variables. The sulfate measurements that Ozkaynak and Thurston used may have been affected by artifacts from the high-volume sampler filters (Lipfert, 1994b); this is also suggested by the fact that their mean $SO_4^{2-}$ value exceeds those of previous years and the mean from the IP data set (compare studies 1 and 9 in Table 12-15).

Ozkaynak and Thurston (1987) ranked the importance of the various pollutants mainly by relative statistical significance in separate regressions. They concluded that the results were "suggestive" of an effect of particles on mortality decreasing with particle size, although in the basic model only $SO_4^{2-}$ was significant. In some of the other models, $PM_{2.5}$ was also significant and $PM_{15}$ nearly so. However, if the effects are judged by elasticities rather than significance levels, $SO_4^{2-}$, $PM_{2.5}$, and $PM_{15}$ would be judged as equivalent, with TSP ranking somewhat lower. The indicated effect of $SO_4^{2-}$ would be reduced from an elasticity of 0.086 to about 0.05 by accounting for filter artifacts (Lipfert, 1994b). Ozkaynak and Thurston (1987) also used source apportionment techniques to estimate that particles from coal combustion and from the metals industry appeared to be the most important.

The coefficients and significance levels obtained for TSP by Ozkaynak and Thurston (1987) may be the result of the TSP data they used, which were based on a single monitoring station in each SMSA and thus are unlikely to be fully representative of population exposures. For example, it is possible that the relatively poor showings of TSP and $PM_{15}$ in their models resulted from the additional measurement error rather than from a difference in underlying toxicity. Ozkaynak and Thurston also noted the need for more elaborate model specifications, larger data bases, and more complete sets of predictor variables, including migration, smoking, and more detailed specification of race and ethnicity. This study did not specifically address the question of lagged pollution variables.

The analysis by Lipfert et al. (1988) comprised a statistical analysis of spatial patterns of 1980 U.S. central city total mortality (all causes), evaluating demographic, socioeconomic, and air pollution factors as predictors (studies 3 to 5 in Table 12-15). The advantages of studying central cities versus SMSAs include potentially better measures of exposure because of the smaller areas, and sufficient numbers of observations to allow analysis of subsets of locations. In this study, sulfate and iron particles were significant (joint) predictors of all-cause mortality in about 180 cities. If the elasticities for $SO_4^{2-}$ were corrected to account for the filter artifacts, they would be reduced by about 50% in this study (i.e., to about 0.01 to 0.05). The data on $PM_{15}$ and $PM_{2.5}$ were only available for 68 cities; neither pollutant was significant in this data set but their elasticities were in the same range found for other pollutants (0.013 to 0.05). This study also allowed a test of lagged pollution data as a means of attempting to distinguish acute from chronic

responses; using 1970 TSP and $SO_4^{2-}$ data to predict 1980 city mortality was slightly less effective than using ca. 1980 data for these pollutants as predictors.

Data from up to 149 metropolitan areas (mostly SMSAs) were analyzed in a study of the relationships between community air pollution and "excess" mortality due to various causes for the year 1980 (Lipfert, 1993). Several socioeconomic models, including the model proposed by Ozkaynak and Thurston (1987), were used in cross- sectional multiple regression analyses to account for non- pollution variable effects (see variables listed for studies 6 to 11 in Table 12-15). Cause-of-death categories analyzed include all causes, nonexternal causes (ICD9 0-800), major cardiovascular diseases (ICD9 390-448), and chronic obstructive pulmonary diseases (COPD) (ICD9 490-96). The patterns for the first three groupings were quite similar but differed markedly from the patterns of COPD mortality, which tend to be higher in the Western United States. Regressions were performed for these cause-of-death groupings as annual mortality rates ("linear" models) and as their logarithms ("log-linear" models). The original regressions used base-10 logarithms; the results have been converted to natural logarithms for this review. Two different sources of measured air quality data were utilized: data from the U.S. EPA AIRS database (TSP, $SO_4^=$, Mn, and $O_3$ from a long-term average isopleth map) and data from the inhalable particulate ($PM_{15}$) network; the latter data ($PM_{15}$,$PM_{2.5}$ and $SO_4^=$ from the IP filters) were only available for 63 locations. All PM data were averaged across all the monitoring stations available for each SMSA; the TSP data were restricted to the year 1980 and were based on an average of about 10 sites per SMSA.

The associations between mortality and air pollution were found to be dependent on the socioeconomic factors included in the models, the specific locations included in the data set, and the type of statistical model used, as was the case with 1970 data (Lipfert, 1984). In the expanded analysis, stepwise regressions were run for each mortality variable and a "parsimonious" model was developed that had statistically significant coefficients for the non-pollution variables. Most of these coefficients also agreed with exogenous estimates of the "correct" magnitudes. Using these models, statistically significant associations were found between TSP and mortality due to non-external causes with the log-linear models evaluated, but not with a linear model. Sulfates, manganese, inhalable particles ($PM_{15}$), and fine particles ($PM_{2.5}$) were not significantly ($P < 0.05$) associated with mortality with any of the parsimonious models, although $PM_{2.5}$ and Mn

were nearly significant in the linear models (p=0.07) and significance may have been affected by the use of smaller data sets. This study showed that $PM_{2.5}$ was the "strongest" particulate variable with linear models, but that TSP performed better in log-linear models. Scatter plots and quintile analyses suggested that a TSP threshold might be present for nonexternal causes and for COPD mortality at around 65 $\mu g/m^3$ (annual average).

This study supported the previous findings of associations between TSP and premature mortality and also the hypothesis that improving the accuracy of pollutant exposure data tends to increase statistical significance. Similarly, the lack of significance for $SO_4^=$ may be partly relate to flawed measurement methods used at the time. The ambiguity between linear and log-linear models probably reflects the effects of influential observations.

***Population-Based Mortality Studies by Age and Cause of Death***

Only a few of the many published ecological mortality studies analyzed subgroups by age and cause. Lave and Seskin (1977) used very broad age groups (0 to 14, 15 to 44, 45 to 64, 65+) with 1960 and 1969 data, which limited the usefulness of the analysis because of the failure to account for age differences within these groupings. Lave and Seskin also examined a large number of disease-specific mortality rates using 1960 and 1961 data. Cancers and cardiovascular diseases were associated with the flawed "minimum" sulfate variable, but respiratory causes tended to be associated with TSP. Lipfert (1978) considered for U.S. cities, 1969 to 1971, infant mortality, ages 1 to 44, and from 45 to 85 by 10-year groups. Very little significance was found below age 65; for ages 75+, $SO_4^{2-}$, TSP, Fe and Mn were significant (one at a time). Lipfert (1978) considered nonexternal causes, total cancers, respiratory cancer, respiratory disease (asthma, bronchitis, emphysema) and all other diseases (mainly cardiovascular). Only Fe was significantly associated with total cancers, only Mn with respiratory cancer, Fe was positively associated with respiratory diseases but $SO_4^{2-}$ was strongly <u>negatively</u> associated with respiratory disease mortality. Lipfert (1993) found that PM was not significantly associated with mortality from major cardiovascular causes for 1980 SMSA mortality, which implies that other causes of death must be involved for this pollutant. Note that between 1960 and 1980 there were major improvements in cardiovascular mortality, resulting in some changes in the geographic patterns. For 1980 SMSA mortality, COPD mortality was strongly associated with TSP with a variety of

regression models. Significant associations were found between TSP and COPD mortality for both linear and log-linear models (study 11 in Table 12-15). When the sulfate contribution to TSP was subtracted, the relationship with COPD mortality was slightly strengthened but no comparable analyses were carried out for coarse respirable particles or for non-sulfate component of fine particles or respirable particles. $PM_{2.5}$ was a significant predictor of heart disease mortality only when the regression model was restricted to the variables used by Ozkaynak and Thurston (1987).

***Cross-Sectional Infant Mortality Studies***

Bobak and Leon (1992) studied neonatal mortality (ages less than 1 month) and post-neonatal mortality (ages 1 to 12 months) from 1986 to 88 in 46 administrative districts in the Czech Republic, in relation to annual averages of $PM_{10}$, $SO_2$, and $NO_2$. The observations comprised 121 combinations of districts and years, ranked into quintiles by mean pollution level for analysis (5 districts had insufficient data). The analysis was ecological in design, in that the outcome variable was the death rate per 1,000 live births and district-wide averages were used as the control variables (mean income, mean savings, mean number of persons per car, proportions of total births outside of marriage, and the rate of legal abortions. In the United States, for example, infant mortality is a strong function of income or poverty status, reflecting the effects of access to pre- and post-natal medical care.

The mean pollutant values were 68.5, 31.9, and 35.1 $\mu g/m^3$ for $PM_{10}$, $SO_2$, and $NO_2$, respectively. This study appears to be based on a denser air monitoring network than many of its predecessors in the U.S.; the mean population per monitor was only about 50,000 and many ecological studies in the U.S. are based on values an order of magnitude higher than this. Two of the three pollutants were highly correlated ($R = 0.80$ for $SO_2$ versus $NO_2$), indicating a common source (combustion). Correlations with $PM_{10}$ were lower (0.15 and 0.26), reflecting the fact that the particle sources were more diverse and included such sources as cement production plants in some districts. The maps presented in the paper suggested little likelihood for spatial autocorrelation, although this topic was not discussed directly. Bobak and Leon (1992) addressed the pollutant collinearity problem by presenting results for each pollutant alone and for

the combination of all three. Results were also presented for analyses with and without socioeconomic adjustments.

The statistics used to indicate significant associations were chi-square p-values for trend across the 5 quintiles, with the relative risks set to 1.0 for the lowest quintiles. Highly significant trends ($p < 0.01$) were seen after socioeconomic adjustment for postneonatal mortality only with $PM_{10}$, even after including the other pollutants. Post-neonatal respiratory mortality showed highly significant trends for all 3 pollutants, but only $PM_{10}$ retained significance ($p=0.013$) with all 3 pollutants. Because of the use of multiple years of data for 41 common locations and the strong likelihood of temporal persistence in annual average air quality, the true number of degrees of freedom may be 41 rather than 121. For this reason, a higher standard of association should be applied to these results ($p < 0.01$ rather than $p < 0.05$). Although Bobak and Leon (1992) elected to analyze their data in terms of linear responses over the entire pollutant range, their results were suggestive of a threshold at the third quintile or higher (mean $PM_{10} = 67\ \mu g/m^3$).

It is not clear from the design of this study whether the reported effects are acute or chronic. Pollution values were averaged over the same years used to aggregate deaths; thus it is possible that exposure did not precede death in all cases. In any event, it may be difficult to distinguish delayed acute from chronic responses for lifetimes as short as a few months. Among the previous U.S. studies reviewed, Lave and Seskin (1977) found infant mortality to be associated with TSP; Lipfert (1978) found marginal significance for the Fe and Mn portions of TSP and a negative association with $SO_4^{2-}$(ca. 1970).

***Summary of Population-Based Cross-Sectional Mortality Studies***

Although most of these studies covered the entire U.S. using the basic paradigm of Lave and Seskin (1970), there are major differences in the degree of confounder control, including the air pollutants investigated. Most of the studies found pollutant elasticities (i.e., mean effects) of 0.02 to 0.08, although the associations with air pollution and specific causes of death varied. However, all of these studies found at least some association between air pollution and mortality on an annual average basis. There was a slight suggestion that elasticities may be decreasing over time (1960 to 1980). It was not possible to determine whether the mortality associations were stronger for pollution measured the same year or in previous years. Analyses by age and cause of

death were limited; the most consistent associations were for the elderly, especially ages 75+, and for respiratory disease mortality and TSP.

Pollutant thresholds were considered by some authors, with mixed success. Studies of 1970 and 1980 SMSA mortality found suggestions of a TSP threshold in the range 60 to 85 $\mu g/m^3$, but perhaps the strongest evidence of a threshold was found for 1980 sulfate, at around 10 $\mu g/m^3$. However, the strong effects that errors in estimated exposures can have on obscuring the true shape of a dose-response function must be considered when evaluating observational evidence for thresholds (see Section 12.2.5).

#### 12.4.1.3 Prospective Mortality Studies

Studies considered here utilized data on the relative survival rates of individuals, as affected by age, sex, race, smoking habits, and certain other individual risk factors. This type of analysis has a substantial advantage over the population-based studies, because the identification of the actual decedents allows stratification according to important individual risk factors such as smoking. Such stratification allows tests of the hypothesis that certain segments of the population may be more sensitive to air pollution than others, which is a major shortcoming of population-based studies. In addition, having data on the actual personal characteristics of each decedent, such as their education or body mass, as opposed to community classification data such as "percent overweight", allows for the possibility of a detailed (i.e., nonlinear) specification of risk factors that is clearly more difficult to assess in a population-based study. However, analyzing individuals also entails dealing with increased variability in outcome and thus requires large sample sizes if effects as small as those typically found in population studies are to be detected with significance. Since none of the prospective cohort studies had data on personal exposures to air pollution, this precludes analysis within cities or by type of exposure (primarily indoor versus outdoor, or coincident versus accumulated, for example). In this limited sense, these studies are also "ecological."

The newer prospective studies (Abbey et al., 1991a; Dockery et al., 1993; and Pope et al., 1995b) are reviewed here. Two older studies, by Morris et al. (1976) and by Kryzanowski and Wojtyniak (1982) are also examples of prospective studies, but without information on respirable

particles, and thus are not discussed. The main findings from the three most recent studies are summarized in Table 12-16.

***California Seventh-Day Adventists***

Abbey et al. (1991a) described a prospective study of about 6,000 white, non-Hispanic, nonsmoking, long-term California residents who were followed for 6 to 10 years, beginning in 1976. The study was designed to test the use of cumulative exposure data as an explanatory factor for disease incidence and chronic effects. Ambient air quality data dating back to 1966 were used, and the study was restricted to those who lived within 5 miles of their current residence for at least 10 years. All of the air quality monitors in the state were used to create individual exposure profiles (duration of exposure to specific minimum concentration levels) for each participant, by interpolating to their zip code centroids based on the 3 nearest monitoring stations. Pollutant species were limited to TSP and $O_3$ in this paper; oxidant concentrations were used in the early part of the monitoring record. Health endpoints evaluated and the numbers of cases included: newly diagnosed cancers (incidence at any site) for males, 115; any cancer site for females, 175; respiratory cancer, 17; definite myocardial infarction, 62; mortality from any external cause, 845; and respiratory symptoms, 272. The Cox proportional hazards model was used, considering age, sex, past smoking, education, and presence of definite symptoms of asthma, chronic bronchitis, or emphysema of airway obstructive disease (AOD) in 1977 as individual risk factors, together with various exposure indices for TSP or $O_3$ (considered separately). Data on occupational exposures and history of high blood pressure were available but were not used in the mortality model. No data were available on climate, body mass, income, migration, physical activity levels or diet. Separate results by gender were not reported for nonexternal mortality.

## TABLE 12-16. PROSPECTIVE COHORT MORTALITY STUDIES

| Source | Health Outcome | Population | Time Period/ No. Units | PM Indicators | PM Mean ($\mu g/m^3$) | PM Range/ (Std. Dev.) | Sites Per City | Total Deaths | Model Type | PM Lag Structure | Other Pollutants | Other Factors | Relative Risk[1] at $SO_4$ = 15, $PM_{15}$ = 50, $PM_{2.5}$ = 25 | RR. Confidence Interval | Elasticity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abbey et al. (1991a) | Total mortality from disease | Calif. 7th Day Adventist | 1977-82 Defined by air monitoring sites | 24 h TSP > 200 | 102 | 25-175 (annual avg) | NA | 845 | Cox proportional hazards | 10 yrs | none | age, sex, race, smoking, education, airway disease | 0.99 TSP[1] | (0.87-1.13)[1] | NS[2] |
| Dockery et al. (1993) | Total mortality | White adult volunteers in 6 U.S. cities[3] | 1974-91 | PM<br>$PM_{2.5}$<br>$SO_4$ | 29.9[13]<br>18<br>7.6 | 18-47<br>11-30<br>5-13 | 1 | 1429 | Cox proportional hazards | none | none | age, sex, smoking, education, body mass, occup. exposure hypertension[4], diabetes[4] | 1.42 $PM_{15}$<br>1.31 $PM_{2.5}$<br>1.46 $SO_4$ | (1.16-2.01)<br>(1.11-1.68)<br>(1.16-2.16) | 0.25<br>0.22<br>0.23 |
| Pope et al. (1995b) | Total mortality | American Cancer Society, adult volunteers in U.S. | 1982-89<br>$PM_{2.5}$ 50 cities<br>$SO_4$ 151 cities | $PM_{2.5}$<br>$SO_4$ | 18.2<br>11[5] | 9-34<br>4-24 | 1<br>1 | 20,765<br>38,963 | Cox proportional hazard | none | none | age, sex, race, smoking, education, body mass, occup. exposure, alcohol consumption, passive smoking, climate | 1.17 $PM_{2.5}$<br>1.10 $SO_4$ | (1.09-1.26)<br>(1.06-1.16) | 0.117<br>0.077 |

[1]For 1,000 h/yr > 200 $\mu g/m^3$.
[2]NS = non significant, confidence limits not shown.
[3]Portage, WI; Topeka, KS; Watertown, MA; Harrisman-Kingston, TN; St. Louis, MO; Steubenville, OH.
[4]Used in other regression analyses not shown in this table.
[5]Value may be affected by filter artifacts.

Of these endpoints, respiratory symptoms and female cancers (any site) were associated with TSP exposure. Neither heart attacks or nonexternal mortality was associated with either pollutant. The authors felt that possible errors in their estimated exposures to air pollution may have contributed to the lack of significant findings, and a later version of the data base include estimates of attenuation resulting from time spent indoors (Abbey et al., 1993), but mortality was not considered in the 1993 paper.

The follow-up analysis (Abbey et al., 1995b) considered exposures to $SO_4^{2-,}$ $PM_{10}$ (estimated from site-specific regressions on TSP), $PM_{2.5}$ (estimated from visibility), and visibility per se (extinction coefficient). No significant associations with nonexternal mortality were reported, and only high levels of TSP or $PM_{10}$ were associated with AOD or bronchitis symptoms.

This study used an unique air quality data base which was developed for the express purpose of studying the effects of long-term cumulative exposures to community air pollution (Abbey et al., 1991b). The technique was shown to provide reliable spatial interpolations that were somewhat better for $O_3$ than for TSP, in keeping with expectations based on the regional nature of $O_3$. TSP may have been an inadequate index of exposure to inhalable particles, especially in this relatively arid region where one might expect to find a large fraction of non-inhalable particles. However, no attention was given to temporal matching of air quality and health; the studies using this data base were intended to evaluate the hypothesis that health is affected by cumulative long-term pollution exposure at some undetermined time, as opposed to acute or coincident exposures. Note that the data base began in 1966 and the mortality follow-up began 10 years later. Because air quality generally improved during this period, the highest concentrations are likely to have occurred in the earlier part of the record, and thus one would not expect spatially-based correlations to also reflect the sum of acute effects, as would be the case when air quality and health data are also matched in time. Note that the range of air quality levels experienced in California from 1966 onward is at least as large as that currently experienced in the rest of the United States, including the nation's highest $O_3$ levels, annual average TSP up to about 175 $\mu g/m^3$, and annual average $SO_4^{2-}$ up to about 9-11 $\mu g/m^3$ (Lipfert, 1978). Thus, lack of adequate range in the pollution variables does not appear to be a valid reason for the lack of statistical significance. However, levels of $SO_2$ and of certain trace metals such as Mn tend to be

lower in California than in the midwestern parts of the United States with larger concentrations of heavy industry.

The finding of Abbey et al. (1991a) of no association between long-term cumulative exposure to TSP or $O_3$ and all natural-cause mortality may be interpreted as showing the absence of chronic responses after 10 years but not necessarily the absence of (integrated) acute responses, since coincident air pollution exposures or integrated exposures over the preceeding few years were not considered. It is also possible that the latency period for chronic effects may exceed 10 years and that additional follow-up might still reveal chronic effects. The magnitudes of the other risk factors considered were not given by Abbey et al. (1991a), which precludes comparison with the other studies.

***Prospective Cohort Study in Six U.S. Cities***

Dockery et al. (1993) analyzed survival probabilities among 8,111 adults who were first recruited in the mid-1970s in six cities in the eastern portion of the United States. The cities are: Portage, WI, a small town north of Madison; Topeka, KS; a geographically-defined section of St. Louis, MO; Steubenville, OH, an industrial community near the West Virginia-Pennsylvania border; Watertown, MA, a western suburb of Boston; and Kingston-Harriman, TN, two small towns southwest of Knoxville. This selection of locations thus comprises a transect across the Northeastern and Northcentral United States, from suburban Boston, through Appalachia, and into the upper Midwest.

The adults were white and aged 25 to 74 at enrollment. In each community, about 2,500 adults were selected randomly, but the final cohorts numbered 1,400 to 1,800 persons in each city (Ferris et al., 1979). Follow-up periods ranged from 14 to 16 years, during which from 13 to 22% of the enrollees died. Of the 1,430 death certificates, 98% were located, including those for persons who had moved away and died elsewhere. However, no information was given in the paper about the actual locations of death. The bulk of the analysis was based on all-cause mortality; no mention was made of subtracting external causes.

These cohorts have been studied extensively for respiratory health (Dockery et al., 1985). Air monitoring data were obtained from routine sampling stations and from special instruments set up by the research team. Individual characteristics of the members (and thus of the decedents)

considered included smoking habits, an index of occupational exposure, body mass index, and completion of a high school education. The Cox proportional hazards model was used to estimate coefficients for the individual risk factors after stratifying by gender and age (5-year groups). The effects of air pollution were evaluated in two ways: by evaluating the relative risks of residence in each city relative to Portage (the city with the lowest pollution levels for most indices), and by including the community-average air quality levels directly in the models. Since only six different long-term average values were available for each pollutant, the effective degrees of freedom are greatly reduced by this procedure.

Most of the air quality measures were averaged over the period of study, in an effort to study long-term (chronic) responses; the specific averaging periods varied by pollutant. Steubenville, Kingston-Harriman, and St. Louis were the most polluted cities and also had the oldest and least educated cohorts and the heaviest rates of smoking among the six cities.

The index of smoking rate used in this study was pack-years, defined as the average number of packs of cigarettes smoked per day times the number of years of smoking. This metric is also a function of age. Current and former smokers were treated separately. This smoking metric assumes that health impacts are defined by cumulative tobacco use rather than by current rate of consumption. The risk per pack-year was higher for former smokers (0.015 per pack year) compared to current smokers (0.01 per pack year); and the finding of a risk per pack year for current smokers that increased with consumption rate suggests that the current rate of smoking may also have merit as a health impact index (especially if the age of starting smoking varies). The total effect of smoking was thus defined as the relative risk of being a smoker plus the risk associated the number of pack-years in question.

The index of socioeconomic status used was having less than a high school education; Rogot et al. (1992a) show that this index is a good measure of mortality differences due to differences in education for white men but not for white women. For women, relative mortality risk continues to increase for educational attainments less than completion of high school. The index of occupational exposure to air pollution (dusts or fumes) did not take into account the length or degree of exposure or the nature of the agents involved. Occupational exposure to dusts or fumes was not found to be a significant risk factor; this outcome may have resulted from

the lack of specificity of the index used. The average percentages having occupational exposure were high, ranging from 28 to 53%, with an average across all cities of 45%.

The index of physiology used was the body mass index (BMI), defined as weight divided by height squared ($kg/m^2$), treated as a linear relationship. The relative risk of increased body mass was similar to that found by Sandvik et al. (1993), where it was not statistically significant, but other investigators have found that the relationship is U-shaped rather than linear and may interact with other risk factors, especially smoking (Grønbæk et al., 1994). Mispecification of a confounder may result in inflation of the effect being evaluated (Klepper et al., 1993) although attenuation of effect sizes is the more typical effect of measurement error.

No consideration was given to possible independent effects of occupation classification, other personal lifestyle variables such as diet or physical activity, migration, or income. Presumably, each subject was characterized by his status at entry to the study; follow-up data on possible changes in risk factors over time were not mentioned. Since the air quality data used in this study were largely obtained from "private" monitoring rather than from public archives, comparisons of the average levels with routine monitoring data were of some interest. No serious disagreements were found, except that it might have been preferable to consider peak rather than average levels of ozone, as has been done in most of the studies of acute effects of ozone on mortality. However, the size-classified particulate data began in 1980 while TSP data began in 1974; from 1974 to 1980 there were large reductions in TSP (and probably in the size-classified particles as well), so that it appears that the size-classified data are less representative of cumulative exposures than TSP. Sulfate appeared to be intermediate in this regard. In this sense, there is a mismatch in time between the air quality data, which were obtained after the study began, and the descriptive data on individuals, which pertain to the period before entry into the study.

A more complete breakdown of relative risk estimates by city, sex, smoking status, education, and body mass index is given in Table 12-17. The mean $PM_{2.5}$ values are provided for reference, but the adjusted relative risks used only age, smoking, education, and body mass as covariates. The RR values for men and women combined are plotted in Figure 12-8 for each pollutant. It should be noted that the apparently linear relationship between fine particles and risk

is less linear if plotted separately for men and for women, but the confidence intervals then become much wider due to smaller samples.

**TABLE 12-17. RELATIVE MORTALITY RISKS IN SIX CITIES**

| | | | Adjusted Risks | | |
|---|---|---|---|---|---|
| Risk Factor | $PM_{2.5}$ Data ($\mu g/m^3$) | Crude Risk | All[2] | Men[2] | Women[2] |
| Residence | | | | | |
| Portage | 11.0 (1980-7)[3] | 1.0[1] | 1.0 | 1.0 | 1.0 |
| Topeka | 12.5 (1980-8) | 0.90 | 1.01 | 1.04 | 0.97 |
| Watertown | 14.9 (1980-5) | 1.16 | 1.07 | 0.94 | 1.22 |
| Harriman | 20.8 (1980-7) | 1.16 | 1.17 | 1.21 | 1.07 |
| St. Louis | 19.0 (1980-6) | 1.48 | 1.14 | 1.15 | 1.13 |
| Steubenville | 29.6 (1980-7) | 1.51 | 1.26 | 1.29 | 1.23 |
| Smoking Status | | | | | |
| Current | | | 1.59 | 1.75 | 1.54 |
| Previous | | | 1.20 | 1.25 | 1.18 |
| No high school education | | | 1.19 | 1.22 | 1.13 |
| Body mass index of 4.5 | | | 1.08 | 1.03 | 1.11 |

[1]Baseline annual crude death rate = 10.73 per thousand population
[2]Adjusted for age, smoking, education, and body mass
[3]Period of $PM_{2.5}$ air monitoring

Source: Dockery et al. (1993)

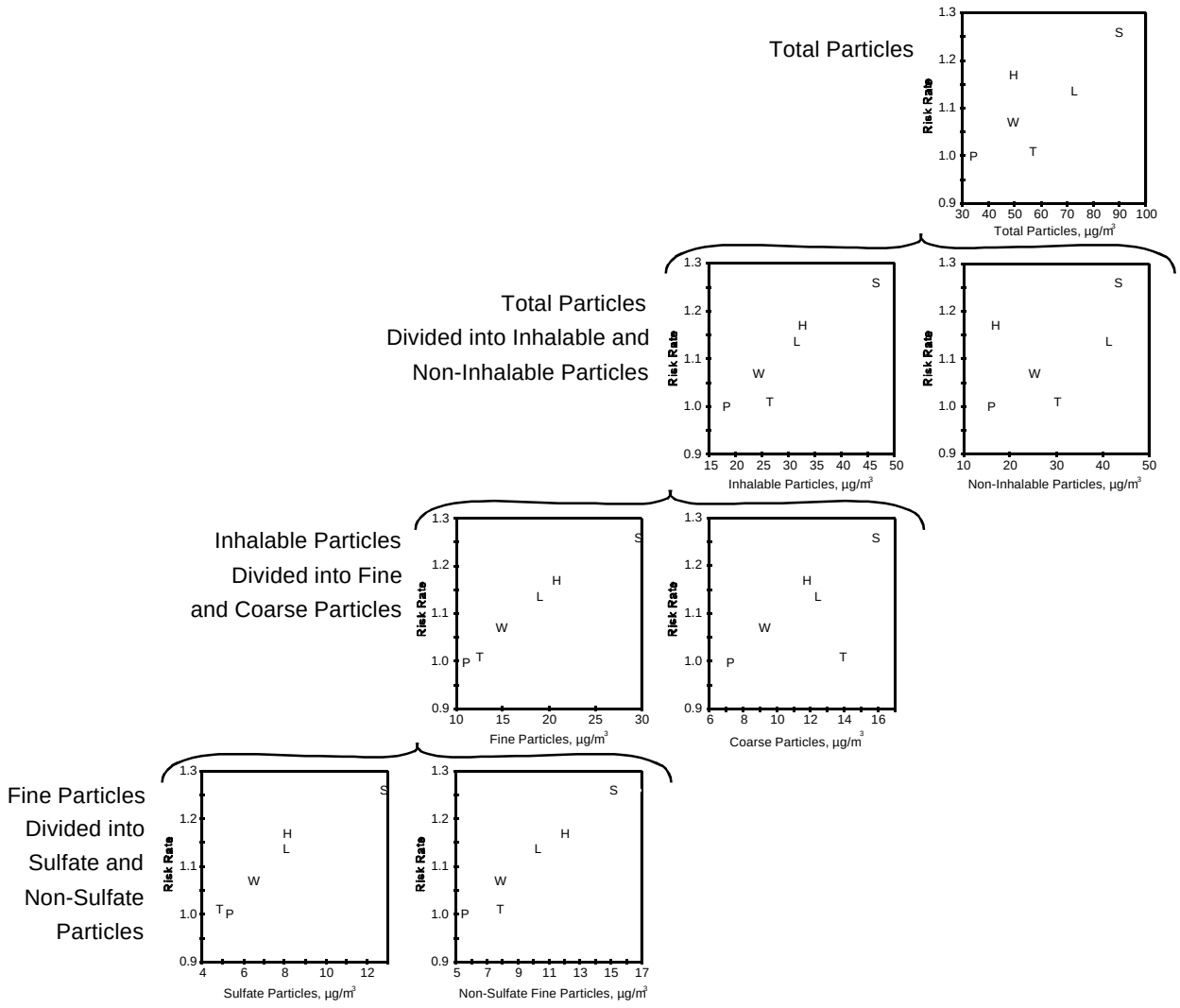


**Figure 12-8. Adjusted relative risks for mortality are plotted against each of seven long-term average particle indices in the Six City Study, from largest range (total suspended particles, upper right) through sulfate and nonsulfate fine particle concentrations (lower left). Note that a relatively strong linear relationship is seen for fine particles, and for its sulfate and non-sulfate components. Topeka, which has a substantial coarse particle component of inhalable (thoracic) particle mass, stands apart from the linear relationship between relative risk and inhalable particle concentration.**

Source: U.S. EPA replotting of results from Dockery et al. (1993).

Based on statewide mortality data, substantial differences in survival rates would be expected across this transect of the Northeastern U.S. and were observed (Table 12-17). The long-term average mortality rate in Steubenville was 16.2 deaths per 1,000 person-years; in Topeka, it was 9.7, yielding a range in average (crude) relative risk of 67% among the six cities. After individual adjustment for age, smoking status, education, and body-mass index, the range in average relative risk was reduced to 26%. The relative importance of the adjustments for age, smoking, education, and body mass in determining the final ranks of the cities may be seen from the table. Also, there is more scatter for men and women separately than when combined, presumably because of the reduction in sample size.

Dockery et al. (1993) report that "mortality was more strongly associated with the levels of fine, inhalable, and sulfate particles" than with the other pollutants, which they attributed primarily to factors of particle size. They provided relative risk estimates and confidence limits based on the differences between air quality in Steubenville and in Portage for these three pollutants. However, it is relatively simple to independently estimate these coefficients from the adjusted risks and pollutants levels in each of the six communities. These estimates correspond quite closely to the figures given by Dockery et al. based on output from the Cox proportional hazards model. However, because there are only 6 different values for the air quality data, the resulting confidence limits are considerably wider than those for the risk factors having individual data. These estimates are given in Table 12-18, as a means of comparing the various pollutants and combination of pollutants. As in the original paper, the relative risks are based on the difference in air pollution between Steubenville and Portage. The data for 1970 TSP (corresponding to a lag of about 12 years) were obtained from Lipfert (1978), assuming that Madison could represent Portage, WI, as was done in the analysis of Schwartz et al. (1996b).

Table 12-18 shows only small differences among many pollutants, including $SO_2$ and $NO_2$, owing in part to the strong collinearity present. Note that TSP and the coarse particle variables created by subtracting $PM_{15}$ from TSP and $PM_{2.5}$ from $PM_{15}$ were not significant, suggesting that particles larger than about 15 $\mu$m in aerodynamic diameter may be less important; this outcome may reflect in part greater spatial variability within the communities for these measures. The non sulfate portion of $PM_{2.5}$ had the tightest confidence limits

**TABLE 12-18. ESTIMATED RELATIVE RISKS OF MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH A RANGE OF AIR POLLUTANTS**

| Species | Regr. Coeff. | Standard Error | Range | Rel. Risk | 95% CIs (n=6) |
|---|---|---|---|---|---|
| $PM_{15}$ | 0.0085 | (0.0026) | 28.3 | 1.27 | (1.04-1.56) |
| $PM_{2.5}$ | 0.0127 | (0.0034) | 18.6 | 1.27 | (1.06-1.51) |
| $SO_4^{2-}$ | 0.0297 | (0.0081) | 8.5 | 1.29 | (1.06-1.56) |
| TSP | 0.0037 | (0.0014) | 55.8 | 1.22 | (0.99-1.53) |
| TSP-$PM_{15}$ | 0.0042 | (0.0032) | 27.5 | 1.12 | (0.88-1.43) |
| $PM_{15}$-$PM_{2.5}$ | 0.0178 | (0.0098) | 9.7 | 1.19 | (0.91-1.55) |
| $PM_{2.5}$-$SO_4$ | 0.0255 | (0.0029) | 8.4 | 1.24 | (1.16-1.32) |
| $PM_{15}$-$SO_4$ | 0.0121 | (0.0034) | 18.1 | 1.24 | (1.05-1.48) |
| $SO_2$ | 0.0093 | (0.0032) | 19.8 | 1.20 | (1.01-1.43) |
| $NO_2$ | 0.0126 | (0.0046) | 15.8 | 1.22 | (1.00-1.49) |
| 1970 TSP | 0.0014 | (0.00044) | 154.0 | 1.25 | (1.03-1.50) |

Source: U.S. EPA recalculations based on results of Dockery et al. (1993).

($SO_4^{2-}$ was multiplied by 1.2 before subtraction, assuming an average composition of $NH_4HSO_4$). Note also that the estimated 1970 TSP variable performed slightly better than the TSP data used by Dockery et al. (ca. 1982) thus suggesting a role for previous pollution exposure. However, all of the differences in relative risks and their confidence limits could have occurred due to chance, given the availability of only 6 observations. Dockery et al. noted that the mean ozone level varied little among cities. This might not have been the case if some measure of peak concentration had been used instead of the overall mean (24-h averages). No relationship was found for aerosol acidity ($H^+$), but only limited data were available. The effects of both sulfate and non-sulfate fine particles seems rather similar, as shown in Figure 12-8. It seems plausible that there may be PM effects related to particle size that are independent of sulfate content or acidity of the particles.

In comparing the most and least polluted cities, Dockery et al. also report elevated risks for cardiopulmonary causes (1.37, [1.11 to 1.68]) and lung cancer (1.37, [0.81 to 2.31], not significant). The relative risk for all other causes of death was 1.01 (0.79 to 1.30). When the six cities were considered individually, only Steubenville showed a statistically significant ($p < 0.05$) elevated risk with respect to the least polluted city (Portage).

Comparison of the pollution risks among the various cohort subsets considered is one of the most important outcomes of a study on individuals. Such comparisons must account for the higher variability among subgroups, however, and the study was not capable of distinguishing excess risks between subgroups less than about 18% (i.e., an excess risk of 1.18 cannot be distinguished from one of 1.36, for example). Although none of these subgroup differences were statistically significant, the mortality risks associated with area of residence (and thus air pollution) were higher for females and for smokers and the risks were also higher for those occupationally exposed compared to the nonexposed. Because of reduced uncertainties about their exposure to air pollution not reflected in the outdoor monitoring data used in this study, it is possible that the relative risk estimates for nonsmokers and the nonoccupationally exposed might be the most reliable estimates (1.19 and 1.17, respectively). See Chapter 7 for a discussion of exposure measurement errors.

In correspondence, Moolgavkar (1994) raised issues of residual confounding, age adjustment and smoking controls. In their response, Dockery and Pope (1994a) agreed that confounding is a potential concern but did not address the possibility that variables other than the ones they considered might be important. They dealt with the age adjustment issue quantitatively and pointed out that the air pollution risk estimates were reasonably stable over different subgroups by smoking status. Age is a potentially important covariate because it measures both susceptibility to health effects and cumulative exposure to pollutants. There is also a possible interaction involving age, air pollution, and time of death, since air pollution concentrations in some communities such as Steubenville and St. Louis decreased substantially during the years preceding and during the period of the study. No use was made of time- and age-dependent cumulative exposure indices in this study.

The authors of this study appear to have made the most of the available individual data on some of the most important mortality risk factors. They were quite cautious in their conclusions,

stating only that the results suggest that fine-particulate air pollution "contributes to excess mortality in certain U.S. cities." There are several other important outcomes:

- None of the population subgroups examined appeared to be significantly more sensitive to air pollution than any other. Since the relative risks were virtually unchanged by excluding subjects with hypertension and diabetes, this finding might also be extended to those with pre- existing chronic diseases. This apparent homogeneity of response has implications regarding the acceptability of population-based studies in which such stratification is not possible.

- The implied regression coefficients are much larger (about an order of magnitude) than those found in either type of cross-sectional study. This could be interpreted as evidence that the population-based studies underestimate the effects, that the chronic effects of air pollution on mortality far exceed the acute effects, or that not all of the spatial confounding has been controlled. Use of linear models for non-linear effects (body-mass index) and failure to control for alcohol consumption, diet, exercise and migration may have contributed to the relatively large effects indicated for air pollution (Lipfert and Wyzga, 1995a).

- If the responses to air pollution truly are chronic in nature, it is logical to expect that cumulative exposure would be the preferred metric (Abbey et al., 1991a). Pollution levels 10 years before this study began were much higher in Steubenville and St. Louis, as indexed by TSP from routine monitoring networks. Estimates of previous levels of fine particles are more difficult, but atmospheric visibility data suggest that previous levels may have been higher in winter, but not necessarily in summer. These uncertainties make it difficult to accept quantitative regression results based solely on coincident monitoring data. For example, annual average TSP in 1965 in Steubenville was about three times the value used by Dockery et al.; use of the older data would have reduced the implied regression coefficients and the relative risks, but not the elasticities. On the other hand, if the responses reflect primarily the last few years of integrated exposure then the concurrent average monitoring data would be reasonably predictive.

Because it seems unlikely that any of the perceived shortcomings of this study could have resulted in bias sufficient to reduce the risk estimates to levels less than those found in acute mortality studies, the study of Dockery et al. (1993) appears to provide support for the hypothesis that the results of long-term air pollution studies must also reflect the presence of acute effects on mortality as integrated over the long term, as suggested by Evans et al. (1984a). It may also be concluded that support has been shown for the existence of chronic effects; these two possibilities are not mutually exclusive. However, these conclusions must be qualified by the realization that

not all of the relevant socioeconomic factors may have been properly controlled in this study. Some quantitative estimates of these effects are given below.

***American Cancer Society Study***

Pope et al. (1995b) analyzed 7-year survival data (1982 to 1989) for about 550,000 adult volunteers obtained by the American Cancer Society (ACS). The Cox proportional hazards model was used to define individual risk factors for age, sex, race, smoking (including passive smoke exposure), occupational exposure, alcohol consumption, education, and body-mass index. The deaths, about 39,000 in all, were assigned to geographic locations using the 3-digit zip codes listed at enrollment into the ACS study in 1982. Relative risks were then computed for 151 metropolitan areas defined by these zip codes and were compared to the corresponding air quality data, ca. 1980. The sources of air quality data used were the EPA AIRS system for sulfates, as obtained from high-volume sampler filters for 1980, and the Inhalable Particulate Network for fine particles ($PM_{2.5}$). The latter data were obtained from dichotomous samplers during 1979-81; Pope et al. used the values from this data base reported by Lipfert et al., 1988 (this study is discussed above), but only 50 $PM_{2.5}$ locations could be matched with the death data. The correlation between the two pollutants was 0.73. The sulfate values from the inhalable particle filters, which are thought to be free from artifacts, were not used in this study. Causes of death considered included all causes, cardiopulmonary causes (ICD-9 401-440, 460-519), lung cancer (ICD-9 162), and all other causes.

This study took great care with the potential confounding factors for which data were available. Several different measures of active smoking were considered, as was the time exposed to passive smoke. The occupational exposure variable was specific to (any of) asbestos, chemicals/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel exhaust, or formaldehyde. The education variable was an indicator for having less than a high-school education. However, alcohol use and body-mass index were considered as linear predictors of survival, whereas other studies have indicated these effects to be non-linear (U or J-shaped) (Doll et al., 1994; Grønbæket al., 1994). Pope et al. (1995b) did not report the relative risk coefficients they obtained for these cofactors, which does not allow comparison of findings for the non- pollution variables with exogenous estimates from independent studies.

Risk factors not considered by Pope et al. (1995b) include income, employment status, dietary factors, drinking water hardness and physical activity levels, all of which have been shown to affect longevity (Sorlie and Rogot, 1990; Belloc, 1973; Pocock et al., 1980). In addition, they did not discuss the possible influences of other air pollutants. For example, Lipfert et al. (1988) found that it was not possible to separate the effects of $SO_2$, $SO_4^{2-}$, and $NO_x$ from one another, and Lipfert (1992) found some evidence for the effects of ozone in cross-sectional mortality regressions for U.S. metropolitan areas in addition to associations between TSP and all-disease and COPD mortality.

The ACS cohort is not a random sample of the U.S. population; it is 94% white and better educated than the general public, with a lower percentage of smokers than in the Six City Study. The (crude) death rate during the 7.25 years of follow-up was just under 1% per year, which is about 20% lower than expected for the white population of the U.S. in 1985, at the average age reported by Pope et al. In contrast, the corresponding rates for the Six- Cities study (Dockery et al., 1993) discussed above tended to be higher than the U.S. average. In spite of these differences, the cause specific ratios for smoking are not signficantly different between the ACS and Six-Cities studies.

No mention was made of residence histories for the decedents; matching was done on residence location at entry to the study. The 1979 to 1981 pollution values were assumed to be representative of long-term cumulative exposures, in keeping with the objective of analyzing chronic effects. However, the previous decade was one of extensive pollution cleanup in most of the nation's dirtiest cities (TSP dropped by a factor of 2 in New York City, for example [Ferrand, 1978]). In contrast, air quality would have remained relatively constant in cities that already met the standards. Thus, it is reasonable to expect that the contrast between "clean" and "dirty" cities would have been greater in 1970 than in 1980. For example, the ranges of TSP and $SO_4^{2-}$ across the U.S. in 1970 were from 40 to 224 and from 3 to 28 $\mu g/m^3$, respectively (Lipfert, 1978). In 1980, these ranges decreased to 41-142 and 2-17 $\mu g/m^3$ (Lipfert, 1993), which suggests that the dirtiest cities became cleaner while the "clean" cities stayed about the same. The change in pollution range is about a factor of 1.8. If the excess mortality found in this study were in fact due to cumulative exposures, the regression coefficients would have been biased upward (in terms of relative risk per $\mu g/m^3$) by using the more recent data. The typically long latency period for

lung cancer (ca. 20 yr.) suggests that data on prior exposures may be particularly important for this cause of death.

The adjusted total mortality risk ratios (computed for the range of the pollution variables) were 1.15 (95% CL = 1.09 to 1.22) for sulfates and 1.17 (95% CL = 1.09 to 1.26) for $PM_{2.5}$. When expressed as log-linear regression coefficients, these values were quite similar for both pollution measures: 0.0070 (0.0014) per $\mu g/m^3$ for $SO_4^{2-}$ and 0.0064 (0.0015) for $PM_{2.5}$, suggesting that particle chemistry may be relatively unimportant as an independent risk factor (it is possible that the $SO_4^{2-}$ results have been biased high by the presence of filter artifacts). Pope et al. (1995b) found that the pollution coefficients were reduced by 10 to 15% when variables for climate extremes were added to the model. Expressed as the percentage of mortality associated with air pollution at the mean values and corrected for filter artifact for $SO_4^{2-}$ using the data of Lipfert (1994c), this study found mean effects of about 5% for sulfate and 12% for $PM_{2.5}$. No significant excess mortality for the "other" causes of death was attributed to air pollution in this study.

Pope et al. (1995b) found very consistent pollution risks for males and females and for ever-smokers and never-smokers for all-cause mortality. However, the relative risks for air pollution were slightly higher for females for cardiopulmonary causes of death. The lung cancer- sulfate association was only significant for males, except for male never-smokers.

The ACS study is unique in having controlled at least partly for passive smoking exposure. Passive smoking results were not reported and compared with the air pollution risks.

The results of the American Cancer Society prospective study were qualitatively consistent with those of the Six City study with regard to their findings for sulfates and fine particles; relative standard errors were smaller, as expected because of the substantially larger database. However, no other pollutants were investigated in the ACS analysis, so that it was not possible to provide the type of pollutant comparison given in Table 12-18. In addition, the ACS regression coefficients were about 1/4 to 1/2 of the corresponding Six City values and were much closer to the corresponding values obtained in various acute mortality studies. Thus it is not clear to what extent chronic effects (as opposed to integrated acute effects) are indicated by these results and to what extent the limited air quality data base used was responsible for this outcome.

***Summary and Conclusions from Prospective Studies***

Table 12-16 summarizes the three newer prospective studies considered here. The California and Six-City studies have relatively small sample sizes and inadequate degrees of freedom, which partially offsets the specificity gained by considering individuals instead of population groups. The two early studies not shown in this table were largely inconclusive and the studies of California nonsmokers by Abbey et al. (1991a, 1995a) that had the spatially most representative cumulative exposure estimates for TSP found no significant mortality effects of previous air pollution exposure. The Six Cities and ACS studies agree in their findings of strong associations between fine particles and excess mortality while the Abbey et al. (1991a, 1995a) studies had no data on fine particles. However, the ACS study did not systematically evaluate the effects of other copollutants. In addition, the timing of the critical exposures remains an open question as does the question of thresholds. It is also important that a range of pollutants be considered in both chronic and acute studies, since it is possible that acute effects may be exhibited by one pollutant and chronic effects by another. Lipfert and Wyzga (1995b) also discuss the studies using elasticity as an index of risk.

### 12.4.1.4 Assessment of Long-Term Studies

***Previous Summaries of Cross-Sectional Studies***

There have been many previous reviews and summaries of air pollution-mortality studies (Ricci and Wyzga, 1983; Lipfert, 1978, 1980b, 1985; International Electric Research Exchange, 1981; Evans et al., 1984b; Lave and Seskin, 1970; Cooper and Hamilton, 1979; Thibodeau et al., 1980; Ware et al., 1981). With respect to cross-sectional studies, Ware et al. (1981) concluded that "...The model can only be approximately correct, the surrogate explanatory variables can never lead to an adequate adjusted analysis, and it is impossible to separate associations of mortality rate with pollutant and confounding variables. This group of studies, in our opinion, provides no reliable evidence for assessing the health effects of sulfur dioxide and particulates...."

***Comparison of Prospective and Population-based Cross-Sectional Study Results***

The literature on long-term health effects of air pollution has been substantially enriched by the publication of the recent prospective studies. Their ability to stratify by smoking habit or

occupational exposure provides valuable information not previously available. These studies also provide a basis with which to evaluate the reasonableness of the "ecologic assumptions" that are required in order to interpret population-based studies. In this section, we consider the two types of studies on an equal footing, following the admonition of Greenland and Robins (1994b) that ecological studies should not be discounted just because they are ecological.

Table 12-19 compares regression coefficients from the two prospective studies that reported significant pollution risks with corresponding estimates made by Lipfert (1993) on an "ecologic" basis, i.e., using SMSA-wide mortality rates. Pope et al. (1995b) introduced this concept by comparing age-race-sex-adjusted SMSA mortality rates with their prospective findings, but without adjusting the SMSA-wide values for cofactors such as smoking or education. They noted the similarity in relative risk estimates between their prospective study findings and the SMSA-wide "ecologic" estimates, but they did not discuss whether the risks predicted by ecological studies would drop substantially if the equivalent confounding variables had been considered in both types of studies. Table 12-19 also makes this comparison and goes on to show how the ecologic estimates of the pollution effects diminish and become negative and/or non-significant as additional cofactors are entered into the regression model. Each of these factors has been shown (by others) to exert an influence on health, and all of them were significant in the ecologic model except drinking water hardness (for which t=1.6). This comparison suggests that the mortality risks assigned to air pollution by the prospective studies may have changed had individual data on additional risk

**TABLE 12-19. COMPARISON OF LOG-LINEAR REGRESSION COEFFICIENTS FROM PROSPECTIVE AND "ECOLOGIC" ANALYSES FOR U.S. METROPOLITAN AREAS**

| Factors Accounted For | $SO_4^{2-}$ coeff. (SE) | FP coeff. (SE) |
|---|---|---|
| A. Prospective studies | | |
| 1. Dockery et al. (1993) | (n=6) | (n=6) |
| **age, sex, active smoking, body mass, education.** | **0.0308 (0.011)** | **0.0124 (0.005)** |
| 2. Pope et al. (1995b) | (n=151) | (n=50) |
| **age, sex, race, active** & passive[a] smoking, education[a], body mass[a], alcohol[a], occupational exposure[a] | **0.007 (0.0014)** | **0.0064 (0.0015)** |
| B. "Ecologic" regressions[b] | (n=149) | (n=63) |
| 1. **age, race** | **0.0092 (0.0019)** | **0.0048 (0.0019)** |
| 2. **age, race,** smoking | **0.0040 (0.00083)** | **0.0048 (0.00195)** |
| 3. **age, race,** smoking, **education** | **0.0058 (0.00195)** | 0.0018 (0.00195) |
| 4. **age, race, smoking, education, migration** | -0.00044 (0.0021) | 0.00012 (0.0016) |
| 5. **age, rage, smoking, education, migration,** drinking water hardness | -0.00055 (0.0021) | 0.00035 (0.0016) |

Bold factors are significant ($p < 0.05$).
[a]Significance of cofactors not stated.
[b]Data from Lipfert, 1993.

factors been available and included in the analysis. If the additional significant risk factors were not confounded with air pollution, then the pollution effect would probably have been found more significant even if unchanged. On the other hand, including correlated risk factors could have either diminished or even increased the estimated effect attributed to air pollution.

It is also interesting that introduction of the smoking variable (statewide cigarette sales) into the ecologic regressions had little or no effect on the pollution coefficients, whereas the other variables had relatively large effects (the correlation between this smoking variable and $SO_4^{2-}$ was

only 0.15). The relative risk corresponding to the ecologic smoking risk coefficient was somewhat less than those found by the prospective studies, probably because this variable is a poor surrogate for individual smoking rates.

Figures 12-9a to 12-9c were prepared to illustrate the overlapping confidence intervals of the various studies using mortality data ca. 1980 and later. For $SO_4^{2-}$, Figure 12-9a, the two prospective studies and Ozkaynak and Thurston's (1987) ecological study overlap, mainly because of the very wide confidence limits of the Six City Study. However, all of these studies accounted for a somewhat limited range of potential confounding variables; the 1980 SMSA study by Lipfert (1993) found $SO_4^{2-}$ to lose significance when additional variables were entered into the model. More overlap is shown for $PM_{2.5}$ (Figure 12-9b), even though significance was not achieved with either ecological study. Overlapping confidence intervals are also seen with TSP (Figure 12-9c), including the California prospective study. These plots thus suggest that much of the apparent contrast among studies could be due to chance variation.

The important contribution of the prospective studies is the proper accounting for individual risk factors, mainly smoking. The question thus arises, could inadequate control for smoking in an ecological study lead to an underestimate of the air pollution relationship? This would require a negative correlation between smoking and air pollution. However, based on state-level data, the correlations between smoking and both $SO_4^{2-}$ and $PM_{2.5}$ are weakly positive. Thus it does not appear that inadequate control for smoking explains the difference in results. One is thus led to the conclusion that either some other factor is negatively correlated with air pollution or that the prospective studies are affected by some confounder that is more important at the individual level than at the community-average level. Of course, much of the range in results seen in these plots could also be due to chance.

***Concluding Discussion***

Referring back to the original goals of long-term mortality studies, several questions appear worthy of reconsideration:

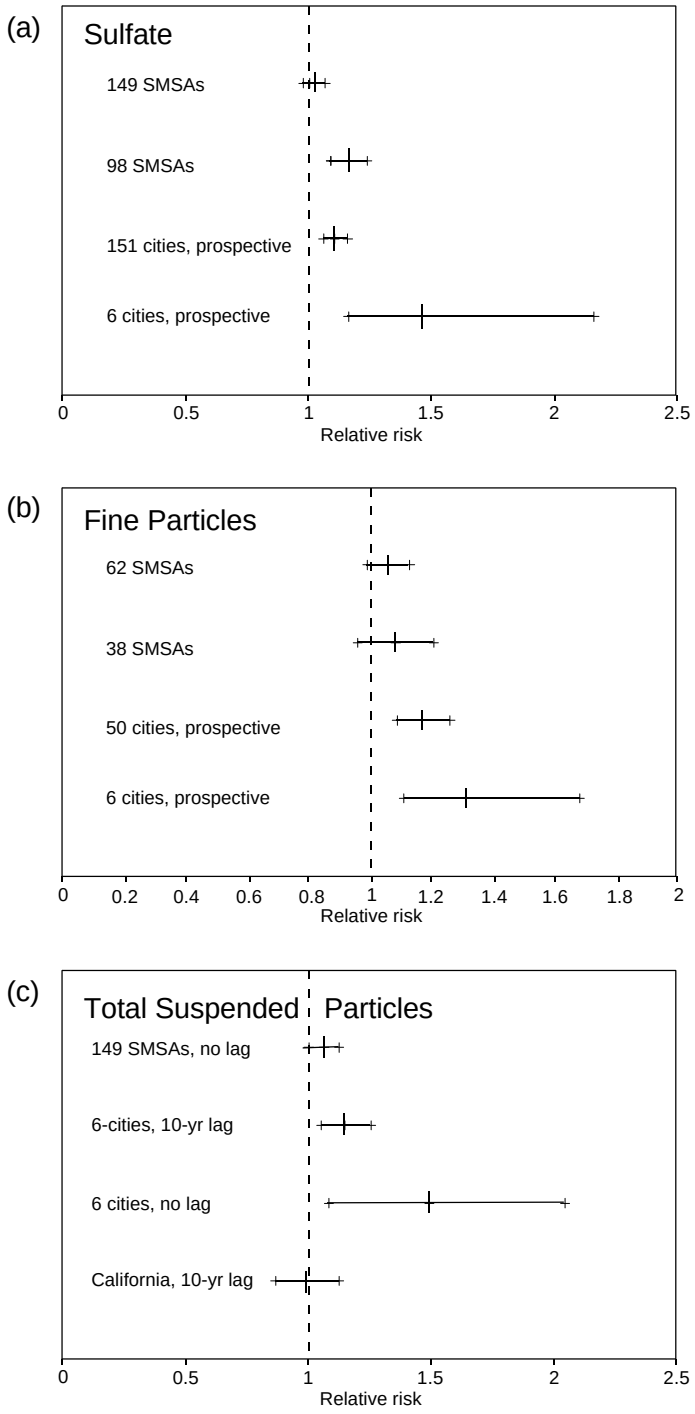


**Figure 12-9. Comparison of relative risks of air pollution exposure in long-term population-based and prospective studies: (a) 15 $\mu$g/m$^3$ sulfate, (b) 25 $\mu$g/m$^3$ $PM_{2.5}$, (c) 100 $\mu$g/m$^3$ total suspended particles.**

Source: Lipfert (1993), Dockery et al. (1993), Ozkaynak and Thurston (1987), Abbey et al. (1993), Pope et al. (1995b).

1. Have potentially important confounding variables been omitted? While many factors are known or believed to affect mortality rates, only those factors that are known to be correlated with air pollution and have effects at least as large as the identified air pollution factors are candidates for omitted significant confounders. Some of these factors were investigated in population-based cross-sectional studies, including selective migration (population loss and gain), lifestyle (diet, physical fitness), socioeconomic status (income, education, occupation associated with potential exposure to air pollution), and other environmental factors (drinking water hardness). As shown in Figure 12-7, including these factors greatly reduces the variability in covariate-adjusted community mortality rates, but does not eliminate the relationship between mortality and long-term fine particle concentrations. Similar adjustments suggest somewhat greater potential for spatial confounding with sulfates in cross-sectional studies than with fine particles. Analyses of the prospective cohort studies have so far included fewer of these factors, and even when the studies have included important individual risk factors such as potential exposure to environmental tobacco smoke, the results for these factors have not yet been reported (Abbey et al., 1991a; Pope et al., 1995b). While it is not likely that the prospective cohort studies have overlooked plausible confounding factors that can account for the large effects attributed to air pollution, there may be some further adjustments in the estimated magnitude of these effects as additional individual and community risk factors are included in the analyses.

2. Can the most important pollutant species be identified? Analyses using data on long-term average concentrations of multiple pollutants have been carried out for many of the population-based cross-sectional studies. Estimates of regression coefficients for PM may be relatively less sensitive to confounding with copollutants in these studies than in the acute mortality studies because there are differences in sources of PM and of other air pollutants across different communities, therefore less collinearity across a spatial cross-section of communities than in air pollution time series data within a particular community. Some investigators have argued that the relative similarity of estimated PM effects in daily time series studies for different communities in which PM is the only air pollutant in the model is an indication that the PM effects are not seriously confounded with those of other air pollutants. However, this argument ignores potential differences in acute vs. chronic effects of different pollutants (see next paragraph).

   The issue of confounding with copollutants has not been resolved for the prospective cohort studies. Abbey et al. (1991a) found no significant association between all-disease mortality and TSP or O3. Dockery et al. (1993) found a very clear gradient of mortality that was rank-ordered with levels of air pollution in six cities, but since many pollutants were similarly rank-ordered across the six cities, it was not possible to say which one(s) were primarily responsible. The best relationships were obtained with fine particles, and almost equally good relationships were found between excess mortality and either sulfate or non-sulfate components of fine particles. However, except for Topeka where the coarse inhalable particles were believed to be primarily of crustal origin, a similarly good relationship was found between excess mortality and inhalable particles or the

coarse particle component of inhalable particles. The ACS study (Pope et al., 1995b) was analysed specifically to test hypotheses about combustion particles, so used only PM2.5 and SO4 as single air pollution indices. Analytical strategies that could have allowed greater separation of air pollutant effects have not yet been applied to the prospective cohort studies.

3. Can the time scales for long-term exposure effects be evaluated? This question has not been resolved by the analyses published so far. Almost all of the population-based cross-sectional studies used long-term average concentrations over the preceding few years or preceding decade, and the few reported analyses on long-term time-lagged exposure were not conclusive. The prospective cohort studies of Abbey et al. (1991a) have also used only long-term community average concentrations. The analyses by Dockery et al. (1993) used only the average pollutant concentrations through the final year of the study period, and it is interesting that the best-fitting pollutants (inhable particles, fine particles, and sulfates) had the shortest period of monitoring data. The ACS (Pope et al., 1995b) pollution data set was even more limited, since only one year of sulfate data was used, and the fine particle data were limited to a subset of the locations used in the sulfate data set and contained only a few years of data.

   Careful review of the published studies indicated a lack of attention to this issue. Long-term mortality studies have the potential to infer temporal relationships based on characterization of changes in pollution levels over time. For example, mortality has the following conceptual time scales:
   - Mortality associated with acute episodic exposures during different seasons;
   - Mortality associated with changes in air pollution due to changes in primary source emissions (for example, Utah Valley in 1987);
   - Mortality associated with sub-chronic exposures over the preceding year or few years;
   - Mortality associated with long-term exposures over the preceding decade or decades.

   Historic air pollution data bases allow construction of air pollution exposure indices at each time scale. For the purposes of such inferences, daily time series, every-other-day time series, every-sixth-day time series, and even monthly time series data could have been used. Furthermore, these time-varying indices could have been constructed using the historic community air pollution data for individual decedents and survivors in the prospective cohort studies, allowing a substantially larger amount of subject-specific air pollution exposure information (in statistical terms, allowing a large number of degrees of freedom for air pollution, rather than just 6 degrees of freedom in the Six City Study for example).

   Published analyses do not allow a clear separation of the short-term and long-term effects of pollution exposure. This also complicates the attribution of mortality to specific pollutants, since excess mortality may be hypothetically attributable to short-term episodic exposures to one pollutant and to long-term or chronic exposures to another pollutant or PM component that may be either an independent additive risk

factor to the short-term pollutant factor, or interactive with the short-term pollutant as a contributing or predisposing factor. Since the different pollutant components may be correlated with each other, the pollutant effects and the time scale effects may be confounded.

4. Is it possible to identify pollutant thresholds that might be helpful in health assessments? Some of the cross-sectional studies have found suggestions of thresholds. However, none of these suggestions can be regarded as robust, and it is possible that uncertainties in the variables selected as proxies for non-pollution effects may have contributed to these findings. Measurement error in pollution variables also complicates the search for potential threshold effects, but the statistical relationship may be stronger and thresholds more easily detected when more reliable exposure data are used in the analyses, for example for those pollutants for which personal exposure and ambient measurements are believed to be more closely related such as sulfates (see discussion in Chapter 7).

   Model specification searches for thresholds have not been reported for prospective cohort studies. The problems of measurement error that complicate threshold detection in the population-based studies have a somewhat different character for the prospective studies. The first problem is that individual risk factors may be measured with error (for example, by failing to report changes in risk factors over time). Another aspect of measurement error is that measured ambient exposures may be correlated with individual risk factors, including indoor air pollution, that also affect health status and potential susceptibility to outdoor air pollution. While only a few such factors can be measured in the daily time series studies (such as age, race, sex, location of residence, place of death), the specification of individual risk factors is one of the principal advantages of the prospective study. Conversely, the possible misspecification or omission of individual risk factors is one of the principal disadvantages of the prospective design, and one the most difficult problems in using epidemiology data to identify thresholds for use in health assessments.

Thus, it appears that, as with most epidemiology, consistency among studies of widely varying design must be sought in order to respond to the shortcomings that were noted earlier, since different designs have different strengths and weaknesses. Among the long-term exposure studies, it is important to find consistency in terms of geographic scale, time periods, pollutant levels, and regional locations. It will also be important to contrast the findings from short- and long- term exposures and to examine coherence among various health endpoints.

At this time, the long-term studies provide support for the existence of short-term PM exposure effects an mortality which may not be completely canceled by decreases below normal rates. They also point toward the likelihood of chronic PM exposure effects above and beyond

the simple summation of acute mortality effects. However, they are equivocal as to all the specific pollutants involved, and they do not exclude the existence of pollutant thresholds, and quantitative estimates of cumulative PM exposure effects beyond acute impacts cannot yet be confidently stated.

## 12.4.2 Morbidity Effects of Long-Term Particulate Matter Exposure

Acute exposures to PM are associated with increased reporting of respiratory symptoms and with small decrements in several measures of lung function (Section 12.3.2.3). As a consequence, cross-sectional studies of the relationship between long-term exposure to PM (or any air pollutant) and consequent chronic effects on respiratory function and/or symptoms may be limited by the inability to control for effects of recent exposures on function and symptoms. Moreover, such studies are further handicapped by: (1) limited ability to characterize accurately lifetime exposure to PM other than through "area-based" ecological assignments or assignments inferred from short-term, acute measurements; (2) their inherent limited ability to characterize correctly other relevant exposure histories (e.g., past histories of respiratory illnesses, passive exposure to tobacco smoke products, active smoking in older subjects); and (3) the fact that the effects to be detected in long term exposure studies may be small in comparison to other sources of variation.

Longitudinal studies offer numerous obvious advantages over cross-sectional studies in terms of characterization of PM exposure and relevant covariates. Nonetheless, to the extent that such studies base their inferences regarding occurrence of long-term morbidity on effects observed over relatively short durations of cohort follow-up (e.g., respiratory illness incidence in relation to ambient PM, short-term relationship between ambient PM and lung function, etc.), their results need to be viewed with circumspection. These approaches do not definitively establish effects of long-term exposure, but only suggest the coherence of the possibility of such long-term effects. Optimal longitudinal studies would provide data on incident chronic conditions such as physician diagnosed asthma and/or evidence for altered patterns of lung function growth and decline for children and adults, respectively. Table 12-20 shows the incidence of selected cardiorespiratory disorders by age and by geographic region.

### 12.4.2.1 Respiratory Illness Studies

***Studies of Children***

The 1982 Criteria Document (U.S. Environmental Protection Agency, 1982a) indicated that apparent quantitative relationships between air pollution and lower respiratory tract illness in children were reported by Lunn et al. (1967), who studied respiratory illnesses in 5- and 6-year old school children living in four areas of Sheffield, England. Positive associations were found between air pollution concentrations and both upper and lower respiratory illness. Lower respiratory illness was 33 to 56% more frequent in the higher pollution areas than in the low-pollution area ($p < 0.005$). Also, decrements in lung function, measured by spirometry tests, were closely associated with respiratory disease symptom rates. Lunn et al. (1970) also reported results for 11-year-old children studied in 1963 to 1964 that were similar to those found earlier for the younger group. On the basis of the results reported, it appears that increased frequency of lower respiratory symptoms and decreased lung function in children may occur with long-term exposures to annual BS levels in the range of 230 to 301 $\mu g/m^3$ and $SO_2$ levels of 181 to 275 $\mu g/m^3$. However, it was noted that these are only very approximate observed-effect levels because of uncertainties associated with estimating PM mass based on BS readings. Also, it could not then be concluded, based on the 1968 follow-up study, that no-effect levels were demonstrated for BS levels in the range of 48 to 169 $\mu g/m^3$ because of: (1) the likely insufficient power of the study to have detected small changes given the size of the population cohorts studied, and (2) the lack of site-specific calibration of the BS mass readings at the time of the later (1968) study. In summary, the Lunn et al. (1967) study provided the clearest evidence cited in the 1982 EPA Criteria Document for associations between both pulmonary function decrements

## TABLE 12-20. INCIDENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE AND BY GEOGRAPHIC REGION (reported as incidence per thousand population and as number of cases in thousands)

| | | Age | | | | Regional | | | |
|---|---|---|---|---|---|---|---|---|---|
| Chronic Condition/Disease | All Ages | Under 45 | 45-64 | Over 65 | Over 75 | NE | MW | S | W |
| COPD | | | | | | | | | |
| Incidence/1,000 persons | 61 | 50 | 63 | 104 | 107 | 56 | 63 | 63 | 61 |
| No. cases × 1,000 | 15,400 | 8,650 | 3,550 | 3,210 | 1,200 | | | | |
| Asthma | | | | | | | | | |
| Incidence/1,000 persons | 49 | 52 | 45 | 40 | 34 | 48 | 49 | 48 | 52 |
| No. cases × 1,000 | 12,370 | 9,000 | 2,180 | 1,230 | 420 | | | | |
| Heart Disease | | | | | | | | | |
| Incidence/1,000 persons | 86 | 29 | 135 | 325 | 404 | 89 | 84 | 93 | 74 |
| No. cases × 1,000 | 21,600 | 5,050 | 6,540 | 10,000 | 4,980 | | | | |
| HD-ischemic | | | | | | | | | |
| Incidence/1,000 persons | 32 | 3 | 61 | 153 | 184 | 37 | 29 | 37 | 24 |
| No. cases × 1,000 | 8,160 | 490 | 2,970 | 4,702 | 2,270 | | | | |
| HD-rhythmic | | | | | | | | | |
| Incidence/1,000 persons | 33 | 20 | 44 | 83 | 104 | 33 | 35 | 32 | 31 |
| No. cases × 1,000 | 8,160 | 3,500 | 970 | 2,550 | 1,275 | | | | |
| Hypertension | | | | | | | | | |
| Incidence/1,000 persons | 111 | 34 | 226 | 358 | 352 | 106 | 115 | 123 | 91 |
| No. cases × 1,000 | 27,820 | 5,830 | 10,980 | 11,000 | 4,300 | | | | |

Source: National Center for Health Statistics (1994c).

and increased respiratory illnesses in children and chronic exposure to specific ambient air levels of PM and $SO_2$.

In another key study reviewed in the second Addendum to the 1982 Criteria Document, Ware et al. (1986) had evaluated respiratory illness and symptoms in children as part of the Harvard Six-City Study. The earlier survey included questions on presence of bronchitis, chronic cough, chest illness, persistent wheeze and asthma. The analysis was restricted to white children (6 to 9 years old) enrolled during one of the first three visits to each city. At least one centrally located air monitoring station established in each community measuring TSP, $SO_2$, water soluble sulfate, $NO_2$, and $O_3$ starting in 1974. The cities of St. Louis, Steubenville and Kingston-Harriman were divided into two regions based on exposure. Multiple logistic regression coefficients were significant for cough, bronchitis, and lower respiratory illness for both TSP and water soluble sulfate. The between city coefficients for TSP ($\mu g/m^3$) were .0101 (.0018) for cough, .0103 (.0046) for bronchitis, and .0076 (.0035) for lower respiratory illness. TSP coefficients for within city analyses tended to be negative.

Dockery et al. (1989) studied respiratory symptoms in 10 to 12 year old white children in the same six U.S. communities as Ware et al. (1986): Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubenville, OH; and Topeka, KS. A cross-sectional survey done in 1980 to 1981 included questions on presence of bronchitis, chronic cough, chest illness, persistent wheeze and asthma. The analysis was restricted to 5,422 white children. Dta on TSP, $SO_2$, $NO_2$, and $O_3$ were obtained from a central air monitoring station in each community starting in 1974. Starting in 1978, dichotomous samplers were used to measure $PM_{15}$. Multiple logistic regression analyses were performed for each health endpoint. The estimated relative odds of bronchitis comparing the most polluted community to the least, was 2.5 (1.1 to 6.1). This corresponded to a 38.7 $\mu g/m^3$ increase in the $PM_{15}$ level. For chronic cough, the odds ratio was 3.7 (1.0 to 13.5); and, for chest illness, it was 2.3 (0.8 to 6.7). The odds ratios corresponding to the other pollutants including TSP, $PM_{2.5}$, sulfate fraction, $SO_2$, $NO_2$, and $O_3$ were not significant, although all were greater than 1.

Data for a cohort of white children aged 7 to 11 from the same Six-City Study were further analyzed by Neas et al. (1994). Respiratory illness history and other background information were collected via a parent-completed questionnaire between September, 1983 and June, 1986.

A stratified one-third random sample of the questionnaire respondents (300 to 350 households per city) was invited to participate in an indoor air quality measurements study. Indoor air quality was measured during two consecutive 1-week sampling periods in both winter and summer; in which respirable particulates ($PM_{2.5}$) and $NO_2$ were measured. Health endpoints reported by questionnaire included shortness of breath, persistent wheeze, chronic cough, bronchitis, asthma, hayfever, earache, and chest illness. Odds ratios (OR) were calculated using multiple logistic regression for an increase of 30 $\mu g/m^3$ in $PM_{2.5}$, after adjusting for gender, age, parental education, parental history of asthma, and city. Most of the health endpoints showed little effect from $PM_{2.5}$ except for bronchitis (OR = 1.18, CI = 0.99, 1.42) and any lower respiratory symptom (OR = 1.13, CI = 0.99, 1.30). However, because no ambient PM data from the Six-City Study were used in the Neas et al. (1994) analyses, the implications of their results for ambient PM exposures are unclear.

Dockery et al. (1996) studied respiratory symptoms among 13,369 white children (8 to 12 years) surveyed between 1988 and 1990 in 24 North American communities chosen based on a gradient of acidic air pollution. Pollutants monitored included particulate acidity, total sulfate, $PM_{2.1}$, $PM_{10}$, $SO_2$, and $O_3$ (Spengler et al. 1996). A two-stage logistic regression model was used to analyze symptoms adjusting for gender, history of allergies, parental asthma, parental education, and current smoking in the home. Children living in communities with the highest levels of particle strong acidity were significantly more likely (OR = 1.66, 95% CI = 1.11, 2.48) to report at least one episode of bronchitis in the past year compared to children living in communities with the lowest levels of acidity. Fine particulate sulfate was also associated with increased bronchitis. For $PM_{2.1}$ and $PM_{10}$, respectively, the odds ratios for bronchitis were 1.50 (95% CI = 0.91, 2.47) and 1.50 (95% CI = 0.93, 2.43), respectively. No other respiratory symptoms were significantly associated with any of the pollutants, including no evidence of asthma or asthmatic symptoms being associated with the measured pollutants. No sensitive subgroups were identified. Strong correlations between several pollutants in this study, especially particle strong acidity in the sulfate (r = 0.90) and $PM_{2.1}$ (r = 0.82), make it difficult to distinguish the indicator of interest.

Stern et al. (1994) studied respiratory illness and lung function in five southwestern Ontario towns (Blenheim, Ridgetown, Tillsonburg, Strathroy, and Wallaceburg) and five in south-central

Saskatchewan (Esterhazy, Melville, Melfort, Weyburn, and Yorkton. Self-administered parental questionnaires were distributed between October 1985 and March 1986. Pollution monitoring started in late 1985 included $SO_2$, $NO_2$, $O_3$, and $PM_{10}$ (measured once every six days in the Ontario towns and every three days in the Saskatchewan towns). Odds ratios were computed (presumably using multiple logistic regression with a random effects model) comparing the endpoints of cough, phlegm, wheeze, asthma, bronchitis, and chest illness for the Ontario towns versus the Saskatchewan towns. No significant differences were found, even after adjusting for gender, parental smoking, parental education, and gas cooking. Actual exposure estimates for the individual towns were not used. The overall mean $PM_{10}$ level for the Ontario towns was 23.0 $\mu g/m^3$ versus 18.0 $\mu g/m^3$ for Saskatchewan.

***Studies of Adults***

The 1982 Criteria Document (U.S. Environmental Protection Agency, 1982a) discussed a series of studies, reported on from the early 1960s to the mid-1970s (Ferris and Anderson, 1962; Kenline, 1962; Anderson et al., 1964; Ferris et al., 1967, 1971, 1976). The initial study involved comparison of three areas within a pulp-mill town (Berlin, New Hampshire). In the original prevalence study (Ferris and Anderson, 1962; Anderson et al., 1964), no association was found between questionnaire-determined symptoms and lung function tests assessed in the winter and spring of 1961 in the three areas with differing pollution levels, after standardizing for cigarette smoking. The study was later extended to compare Berlin, NH, with the cleaner city of Chilliwack, BC, in Canada (Anderson and Ferris, 1965). The prevalence of chronic respiratory disease was greater in Berlin, but the authors concluded that this difference was due to interactions between age and smoking habits within the respective populations.

The Berlin, NH, population was followed up in 1967 and again in 1973 (Ferris et al., 1971, 1976). During 1961 to 1967, all measured indicators of air pollution fell (e.g., TSP from about 180 $\mu g/m^3$ in 1961 to 131 $\mu g/m^3$ in 1967). In the 1973 follow-up, sulfation rates nearly doubled from the 1967 level (0.469 to 0.901 mg $SO_3/100\ cm^2$ day) while TSP values fell from 131 to 80 $\mu g/m^3$. Only limited $SO_2$ data were available (i.e., the mean of a series of 8-h samples for selected weeks.) During the 1961 to 1967 period, standardized respiratory symptom rates decreased and lung function also improved. Between 1967 to 1973, age-sex standardized respiratory symptom

rates and age-sex-height standardized pulmonary function levels were unchanged. Although some of the testing was done during spring versus summer in different comparison years, Ferris and coworkers tried to rule out seasonal effects by retesting some subjects in both seasons during one year and found no significant differences in test results. Given that the same set of investigators, using the same standardized procedures, conducted the symptom surveys and pulmonary function tests over the entire course of these studies, it is unlikely that the health endpoint improvements seen in the Berlin study population were due to variations in testing procedures; rather, they appear attributable to decreases in TSP levels from 180 to 131 $\mu g/m^3$. The relatively small changes observed and limited aerometric data available, however, argue for caution in placing much weight on these findings as quantitative indices for effect or no-effect levels for health changes in adults associated with chronic exposures to PM measured as TSP.

The earlier 1982 criteria review (U.S. Environmental Protection Agency, 1982a) also assessed a cross-sectional study conducted by Bouhuys et al. (1978) in Ansonia (urban) and in Lebanon (rural), two Connecticut towns in which differences in respiratory and pulmonary function were examined in 3,056 subjects (adults and children). No differences were found between Ansonia and Lebanon for chronic bronchitis prevalence rates, but a history of bronchial asthma was noted as being highly significant for male resident of Lebanon (the cleaner town) as compared to Ansonia (the higher-pollution area). Nor were any significant differences observed between the communities for pulmonary function tests adjusted for sex, age, height and smoking habits. However, prevalence for three of five symptoms (cough, phlegm, and plus one dyspnea) were significantly ($p < 0.001$) higher for adult non-smokers in Ansonia. Overall, the mix of positive and negative health effect results make it difficult to interpret this cross-sectional study.

Numerous published studies have attempted to relate chronic respiratory health effects to ambient pollutants such as PM and $O_3$ (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b; 1995a,b,c). From among these, the series of publications from the Adventist Health Smog Study (AHSMOG) (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b) are discussed first below.

The basic population for these studies represents California-resident, Seventh-Day Adventists aged 25 years who had lived 11 years or longer (as of August 1976) in either a high-oxidant-polluted area (the South Coast Air Basin encompassing Los Angeles and vicinity and a

portion of the nearby Southeast Desert Air Basin) or a low-pollution area (San Francisco or San Diego). This sample was supplemented by an additional group of subjects who met the 11-year residence requirement but came from low-exposure rural areas in California. The total baseline sample (March 1977) comprised 8,572 individuals, of whom 7,267 enrolled. From this group, 109 current smokers and 492 subjects who had lived outside of the designated areas for a portion of the previous 11 years were excluded. Detailed respiratory illness and occupational histories were obtained. In these studies, "COPD" refers to "definite chronic bronchitis", "definite emphysema", and "definite asthma" as defined by the study questionnaire. Measures of pulmonary function are not included.

California Air Resources Board (CARB) air monitoring system data for total oxidants, $O_3$, TSP, $SO_2$, $NO_2$, CO, and $SO_4$ (excluding 1973 to 1975) were used. Most (99%) of the subjects (excluding the rural supplement) lived close enough to the nearest CARB monitoring site to consider the CARB data as relatively reliable concentration estimates for the above listed ambient pollutants at their residence. Concentrations at the monitors were interpolated to the centroid of each residential zip code from the three nearest monitoring sites with the use of a $1/R^2$ interpolation. Subsequent development of exposure indices took account of improvements in CARB data after 1973.

The initial report from this study (Hodgkin et al., 1984) was summarized in the 1986 Ozone Criteria Document (U.S. Environmental Protection Agency, 1986c). Based upon a multiple logistic regression that adjusted for smoking, occupation, race, sex, age, and education, it was estimated that residence in the South Coast Air Basin conferred a 15% increase in risk for prevalent COPD. No estimates of exposure were provided, and the data were considered to be of limited utility.

Next, Euler et al. (1988) assessed the risk of chronic respiratory disease symptoms due to long-term exposure to ambient levels of TSP, oxidants, $SO_2$, and $NO_2$. Symptoms were ascertained for 8,572 Southern California Seventh-Day Adventists (nonsmokers—25 years and older) who had lived 11 years or longer in their 1977 residential area by using the National Heart, Lung, and Blood Institute questionnaire. Tobacco smoking (active and passive) and occupational exposures were assessed by questionnaires, as were lifestyle characteristics relative to pollution exposure (e.g., such as time spent outside and residence history). For each of the 7,336

participants who responded and qualified for analysis, cumulative exposures to each pollutant were estimated using monthly residence zip code histories and interpolated exposures from state air monitoring stations.

Multiple logistic regression analyses were conducted for pollutants individually and together with eight covariables (environmental tobacco smoke exposure at home and at work, past smoking, occupational exposure, sex, age, race, and education). Statistically significant associations with chronic respiratory symptoms were seen for: (a) $SO_2$ ($p = 0.03$), relative risk of 1.18 for 13% of the study population with 500 h/year of exposure above 0.04 ppm; (b) oxidants ($p < 0.004$) relative risk of 1.20 for 18% with 750 h/year above 0.1 ppm; and (c) TSP ($p < 0.00001$), relative risk of 1.22 for 25% with 750 h/year above 200 $\mu g/m^3$. When these pollutant measures were analyzed together, only TSP showed statistical significance ($p < 0.01$). Persons working with smokers for 10 years had relative risks of 1.11 and those living with a smoker for 10 years had relative risks of 1.07.

Major improvements in the exposure assessment methods used were presented by Abbey et al (1991a). Previous exposure estimates were refined by computation of "excess concentrations" (concentration minus cutoff, summed over all relevant time periods and corrected for missing data). Exposures also were corrected for time spent at work and time away from residence, with estimates provided for the environments where work occurred and for geographic areas away from residence. The quality of the interpolations (in terms of distance of monitor from residence zip codes) was also evaluated and incorporated into the estimates. Adjustments were made for time spent indoors by individuals and new indices were developed that were based on $O_3$, rather than on total oxidants. Comparison of actual versus interpolated cumulative exceedance frequencies and mean concentrations at monitoring stations (1985 through 1986) for TSP and $O_3$ were assessed. The actual versus interpolated 2-y mean concentrations did not differ significantly and were correlated with a Pearson correlation coefficient of 0.78 for TSP and 0.87 for $O_3$.

The above estimates were applied to data that included 6 years of follow-up of the study population (Abbey et al., 1991b). This analysis focused on incident occurrence of obstructive airways disease (AOD—same definition as for COPD above). Incident symptoms of AOD were significantly associated with hours above several TSP thresholds, but not with hours above any

$O_3$ threshold (i.e., above 10 pphm ozone - OZ (10)). Incidence of definite symptoms of AOD and chronic bronchitis were statistically significantly ($P < 0.05$) elevated for average annual hours in excess of 100, 150, and 200 $\mu g/m^3$, i.e., TSP (200), and mean concentrations of TSP but not for 60 $\mu g/m^3$. For incidence of asthma, significantly elevated risks were found only for average annual hours above thresholds of 150 and 200 $\mu g/m^3$, i.e., TSP (200). Relative risks for concentrations above 200 $\mu g/m^3$ of TSP for bronchitis were 1.33 (95% CL = 1.07 to 1.81); and for asthma 1.74 (95% CL = 1.11 to 2.92). Cumulative incidence estimates were adjusted with the use of Cox proportional hazard models for the same variables noted in the original publication of Hodgkin et al. (1984), as well as the presence of possible symptoms in 1977 and childhood respiratory illness history. None of the analyses included both $O_3$ and TSP thresholds. No data were provided on demographics of subjects available for the prospective analysis and their representativeness versus the entire base population.

Another analysis by Abbey et al. (1993) evaluated changes in respiratory symptom severity with the TSP and $O_3$ thresholds noted above. In this analysis, logistic regression, rather than Cox proportional hazard modeling, was used to assess cumulative incidence of components of the COPD/AOD complex; and multiple, linear regression was used to evaluate changes in symptom severity. When $O_3$ was considered alone, there was a trend toward increased risk of asthma for a 1,000-h average annual increment in the OZ (10) criterion (RR = 2.07, 95% CL = 0.98 to 4.89). This analysis suggested that recent ambient $O_3$ concentrations were more related to cumulative incidence than past concentrations. Change in asthma severity score was significantly associated with the 1977 to 1987 average annual exceedance frequency for $O_3$ thresholds of 10 and 12 pphm. No significant effects were found for COPD or bronchitis alone. In contrast to the above study of cumulative incidence, another analysis was done in which TSP (200) and OZ (10) were allowed to compete for entry into a model to evaluate asthma cumulative incidence and changes in severity. In the cumulative incidence model using exceedance frequencies (number of hours above threshold), TSP (200) entered before OZ (10); when average annual mean concentrations were used, $O_3$ entered before TSP. From this, the authors concluded that both TSP and $O_3$ were relevant to asthma cumulative incidence. In no case did both pollutants simultaneously remain significant in the same regression, and no interactions between TSP and $O_3$ were found for either metric. A similar result was found for change in asthma severity. As in previous analyses, TSP

(200) and OZ (10) exceedance frequencies (0.72) were highly correlated with their respective average annual mean concentrations (0.74).

Abbey et al. (1995a) analyzed the same cohort for development of airway obstructive disease (AOD), bronchitis, and asthma for the 1977 to 1987 period. Levels of TSP were monitored from 1973 to 1987; $PM_{10}$ was estimated from site/seasonal-specific regressions on TSP for 1973 to 1987; and fine particles ($PM_{2.5}$) were estimated from airport visibility data for 1967 to 1987. Relative risks near 1.4 were found for areas with 42 days/year of TSP levels above 200 $\mu g/m^3$ and relative risks near 1.2 were found for 42 days/year of $PM_{10}$ levels above 100 $\mu g/m^3$. The relative risks for an average annual increase of $PM_{2.5}$ above 45 $\mu g/m^3$ were not statistically significant. The use of cut-points makes it difficult to derive quantitative relationships between the health effects and the pollutants. Also, the authors note that the effects of TSP, $PM_{10}$, and $PM_{2.5}$ cannot be truly separated in this study since $PM_{10}$ and $PM_{2.5}$ were indirectly estimated, whereas TSP was actually monitored and, also, because of the high correlation between them.

Abbey et al. (1995b) reanalyzed the same data using estimated concentrations as described by Abbey et al. (1995c). The same three dependent variables, AOD, bronchitis, and asthma, were used in the analysis along with the covariates of age, education, gender, and previous symptoms. The effect of $PM_{2.5}$ on new AOD was an estimated relative risk of 1.46 (95% CI of 0.84 to 2.46), and the effect on new bronchitis was 1.81 (95% CI of 0.98 to 3.25). Relative risks using $PM_{10}$ and TSP were not given, but reported t-values suggested that TSP and $PM_{10}$ were better predictors of all three endpoints. The authors attributed this difference to measurement error because all three pollutant measures were highly correlated.

Schwartz (1993b) analyzed data on respiratory illness diagnosed by a physician from the NHANES survey conducted from 1971 to 1974 on the non-institutionalized U.S. population aged 1 to 74. The survey used a complex design and the Schwartz analysis was restricted to 53 urban sampling units. Endpoints included asthma, bronchitis, respiratory illness and dyspnea. EPA's SAROAD data base was used to obtain data from population oriented monitors in the 53 areas. Average TSP concentrations ($\mu g/m^3$) for previous years were used as the exposure measure. No other pollutants were considered. Multiple logistic regression analysis was used that included terms for cigarette consumption per day, former smoking, age, race, and gender. The coefficient

for chronic bronchitis was .0068 (.0023) and for respiratory illness it was .0058 (.0019) (change in OR per $\mu g/m^3$ TSP). The coefficients were slightly larger when restricted to non-smokers.

Yano et al. (1990) studied chronic respiratory illness in females aged 30 to 59 in two cities in Japan. One city, Kanoya is 25 km from an active volcano, and the other, Tashiro, is 50 km from the volcano. Winter concentrations of TSP in Kanoya average 341 $\mu g/m^3$, whereas they average 119 $\mu g/m^3$ in Tashiro. Respiratory conditions were assessed using a Japanese version of the ATS-DLD questionnaire. No significant difference in rates of bronchitis, asthma, wheezing, or other related illnesses were found.

Ishikawa et al. (1969), which was reviewed in U.S. EPA (1982a), assessed the prevalence and severity of pulmonary emphysema by examining a series of postmortem lungs obtained from long-time residents in two cities: heavily industralized urban St. Louis, MO and agricultural Winnipeg, Canada. Three hundred adult lungs were collected for each city during the years 1960 to 1966. No attempt to correlate clinical signs and symptoms with pathoanatomic changes was undertaken. Air pollution emissions in one-thousand tons per year for sulfur oxides, nitrogen oxides, hydrocarbons, and "particulates" were respectively, 455, 138, 374, and 147 in St. Louis; and were respectively 36, 20, 62 and 82 on Winnipeg. In neither city were cases of severe emphysema observed in nonsmokers. There was more emphysema in the study in St. Louis than in Winnipeg, but the study does not provide any way to credibly associate the health observations specifically with PM exposure. Other more elevated pollutants or other factors may have played a role.

Some researchers used case-control approaches to study chronic respiratory system health effects in relationship to ambient pollutants such as PM. For example, Tzonou et al. (1992) studied the relation of urban living and tobacco smoking to COPD development in Athens, Greece. Their findings suggested that air pollution or another aspect of the urban environment can be an important contribution to the development of COPD. Specific PM levels were not studied. Katsouyanni et al. (1991) conducted a case-control study in Athens exploring the role of smoking and outdoor air pollution and their relationship to lung cancer. Air pollution levels were associated with an increased risk for lung cancer but the relative risk was small and not statistically significant. Xu et al. (1989) studied air pollutants and lung cancer in China and their findings suggested that smoking and environmental pollution combined to allow for elevated rates

of lung cancer mortality. In Poland, Jedrychowski et al. (1990) found similar findings as the above studies.

Rothman et al. (1991) reported that wildland firefighters experience a small cross-seasonal decline in pulmonary function and an increase in several respiratory symptoms. Hours of self-reported fire-fighting activity were used as a surrogate for fire smoke exposure. At wildland fires, concentrations of a variety of pulmonary irritants (including respirable PM, acrolein and formaldehyde) often exceed Occupational Safety and Health Administration (OSHA) permissible exposure limits. In a study by Shusterman et al. (1993) on smoke-related disorders in Alameda County, CA related to an October 20, 1991 grass fire in the Oakland-Berkeley hills, bronchospaitic and irritative reactions to smoke constituted more than half of the medical emergency visits related to the fire. Many of these patients had a history of asthma.

***Chronic Respiratory Disease Studies Summary***

The first three studies in Table 12-21 were based on a similar type of questionnaire but were done by Harvard University at three different times as part of the Six-City and 24-City Studies. The studies provide data on the relationship of chronic respiratory disease to PM.

## TABLE 12-21. CHRONIC RESPIRATORY DISEASE STUDIES

| Study | PM Type & No. Sites | PM Mean & Range | Overall Symptom Rate | Model Type | Other pollutants measured | Other Covariates | Other pollutants in model | Result* (Confidence Interval) |
|---|---|---|---|---|---|---|---|---|
| Ware et al. (1986) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1974-1977 | Daily monitoring of TSP, $SO_2$, $O_3$, and $NO_2$, at each city | City TSP means ranged from 39 to 114 µg/$m^3$ | Cough, .08, Bronchitis .08, Lower resp. .19 | Logistic regression | $SO_2$, $NO_2$, and $O_3$ | Age, gender, parental education, maternal smoking | none | Cough 2.75 (1.92, 3.94) Bronchitis 2.80 (1.17, 7.03) Lower resp. 2.14 (1.06, 4.31) |
| Dockery et al. (1989) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1980-1981 | Daily monitoring of $PM_{15}$, sulfate fraction at each city | City $PM_{15}$ means ranged from 20 to 59 µg/$m^3$ | Cough, .02 to .09, Bronchitis .04 to .10, Lower resp. .07 to .16 | Logistic regression | $SO_2$, $NO_2$, and ozone | Age, gender, maternal smoking | none | Cough 5.39 (1.00, 28.6) Bronchitis 3.26 (1.13, 10.28) Lower resp. 2.93 (0.75, 11.60) |
| Dockery et al. (1996) Study of children aged 8 to 12 in 24 communities in the U.S. and Canada. | $PM_{10}$, $PM_{2.1}$, sulfate, fine particle acidity | $PM_{10}$ 26.3, range from 17.9 to 35.2 $H^+$ 27.5 nmoles/$m^3$, range from 0 to 51.9 | Not given | Multiple logistic regression | $SO_2$, $O_3$, $NH_4$, $HNO_2$, $HNO_3$ | Gender, history of severe chest illness, humidifier, environ. tobacco smoke, year of study | | Bronchitis OR = 1.66 for range of particle strong acidity, OR = 1.65 (1.12, 24.2) for sulfate |
| Abbey et al. (1995a,b,c) Study of bronchitis, AOD, and asthma in Seventh Day Adventist adults | Daily monitoring of TSP, $PM_{10}$ (visibility at 9 sites in no. and so. California) | Not given | AOD = 11.8% Bronchitis = 7.2% | Multi-logistic regression | $SO_4$, $O_3$, $SO_2$, $NO_2$ | Age, gender, education, previous symptoms | none | 1.23 AOD (0.91, 1.65) 1.39 Bronchitis (0.99, 1.92) |

*Estimates calculated from data tables assuming a 50$\mu$g/$m^3$ increase in $PM_{10}$ or 100 $\mu$g/$m^3$ increase in TSP.

All three studies suggest a chronic effect of PM on respiratory disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio = 1.66) in the community with highest exposure of particle strong acidity when compared with the least polluted community. Fine particulate sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

The study of Abbey et al. (1995a,b,c) was done in California and showed results in the range of other studies. These studies suffer from the usual difficulty of cross sectional studies. Evaluation of PM effects is based on variations in exposure determined by a different number of locations. In the first two studies, there were six locations and in the third there were four. The results seen in all studies were consistent with a PM gradient, but it is impossible to separate out effects of PM and any other factors or pollutants which have the same gradient.

#### 12.4.2.2 Pulmonary Function Studies

***Studies of Children***

Ware et al. (1986) studied lung function in children in early years of the Harvard Six Cities Study. A cross-sectional survey was done between 1974 and 1977. Lung function was measured at the time of the survey using a water filled recording spirometer. $FEV_{1.0}$ and FVC measurements were used in the analyses. Starting in 1978, dichotomous samplers were used to measure $PM_{10}$. Adjusted logarithms of the pulmonary function values were not related to TSP concentrations. The change in $FEV_{1.0}$ per $10\mu g/m^3$ change in TSP was .06% (.17%) at the first examination and -0.09% (.17%) at the second.

Dockery et al. (1989) also studied lung function in 10 to 12-year-old white children in the same six cities as noted above. Lung function was measured, using a water filled recording spirometer, at the time of a cross-sectional survey done in 1980 to 1981. The analysis was restricted to 5,422 children. In each community, a centrally located air monitoring station measured TSP, $SO_2$, $NO_2$, and $O_3$, starting in 1974; and dichotomous samplers were used to measure $PM_{10}$ starting in 1978. Separate regressions of adjusted city-specific pulmonary function

levels on air pollution for children with and without asthma or wheeze did not show any associations.

Neas et al. (1994) analyzed a cohort of white children aged 7 to 11 from the same six cities for pulmonary function, using 1983 to 1988 data on: FVC; $FEV_{1.0}$; the ratio of $FEV_{1.0}$ to FVC; $FEF_{25-75}$; and the ratio of $FEF_{25-75}$ to FVC. The regression model used the logarithm of the lung function value as the dependent variable and included gender, parental education, history of asthma, age, height, weight, and city as covariates. No statistically significant indoor $PM_{2.5}$ effects on lung function were found. The use of logarithms of the dependent variables, as well as the lack of overall mean lung function values, makes it impossible to directly compare the results of this study with those of others.

Stern et al. (1994) studied lung function and respiratory illness in five towns each in southwestern Ontario (Blenheim, Ridgetown, Tillsonburg, Strathroy, and Wallaceburg) and in south-central Saskatchewan (Esterhazy, Melville, Melfort, Weyburn, and Yorkton). Lung function measurements were made and self-administered parental questionnaires were given between October 1985 and March 1986. Pollution monitoring was not begun until late 1985, and included $SO_2$, $NO_2$, and $O_3$. $PM_{10}$ was measured once every six days in the Ontario towns and every three days in the Saskatchewan towns. Lung function measurements included FVC, $FEV_{1.0}$, PEFR, $FEF_{25-75}$, and $V_{50}$max, and were adjusted for age, gender, weight, standing height, parental smoking, gas cooking, and standing height by gender interaction. Ontario children had statistically significant decrements in FCV (1.7%) and $FEV_{1.0}$ (1.3%) compared with Saskatchewan children, but no differences were found in the flow parameters. Actual exposure estimates for the individual towns were not used. The overall mean $PM_{10}$ level in the Ontario towns was 23.0 $\mu g/m^3$ compared with 18.0 $\mu g/m^3$ for Saskatchewan.

Spektor et al. (1991) studied pulmonary function in children living in Cubatao, Brazil. $PM_{10}$ and $SO_2$ measurements were made at six sites in Cubatao, located about 44 km from Sao Paulo. Average annual $PM_{10}$ levels ranged from 43 to 140 $\mu g/m^3$. Pulmonary function measurements were made monthly from March to November, 1988. Individual regressions were performed using height, weight, and pollution as covariates, and average slopes were reported for each of six schools, but no confidence intervals were given. Both $FEV_{1.0}$ and PEFR were significantly related

to $PM_{10}$ at the six schools. The average decrease in PEFR per 50 µg/$m^3$ was about 100 ml/sec, a value much larger than those seen in other studies.

During 1988, He et al. (1993) studied lung function in children in areas of Wuhan, China. The children (aged 7 to 13 years) were from six urban and one suburban school. Pollution measurements for TSP, $SO_2$, CO, and nitrogen oxides were collected by the Wuhan Environmental Protection Agency Air Pollution Monitoring Network from 1981 to 1988. All pollutants were higher at the urban site, with TSP values averaging 251 $\mu$g/$m^3$ as compared to 100 $\mu$g/$m^3$ at the suburban site. The cross sectional study was conducted in May and June of 1988. The hypothesis was that the relationship between lung function and height would be less in the urban city. Lung function growth curves were constructed by regressing $FEV_{1.0}$ and FVC on height for males and females for both areas. The curves were significantly steeper for the suburban children than for the urban children.

Arossa et al. (1987) studied lung function in approximately 2000 children in Turin, Italy, during a time period when both TSP and $SO_2$ were being reduced. Three areas of Turin (central city, peripheral area, and suburban area) were studied during the winters of 1980 to 1981 and 1982 to 1983. Each child's respiratory health was assessed at the beginning and end of the study using a questionnaire which also obtained demographic information. Lung function measurements included FVC, $FEV_{1.0}$, $FEF_{25-75}$, and $MEF_{50}$. Daily $SO_2$ and TSP measurements were available from seven monitoring sites in the area. The pollution data confirmed that the large $SO_2$ differences across areas in 1980 to 1981 were reduced substantially by 1982 to 1983. The differences in TSP remained small but constant during the time period. A general linear model analysis was used to calculated adjusted lung function values. From these values, individual slopes were estimated and these became the unit of analysis. Average slopes were significantly higher within the city of Turin when compared with the suburban area, suggesting to the authors that a decrease in pollution (primarily $SO_2$) resulted in an improvement of lung function.

Raizenne et al. (1996) studied pulmonary function test results from 22 North American communities chosen so that there was a gradient of acidic air pollution. Pollutants monitored included particulate acidity, total sulfate, $PM_{2.1}$, $PM_{10}$, $SO_2$, and $O_3$ (Spengler et al., 1996). Parents of children aged 8 to 12 years of age were surveyed between 1988 and 1990, and pulmonary function tests were administered in each community to coincide with the last two

weeks of the year-long air monitoring period. A two-stage regression analysis that adjusted for age, gender, weight, height, and gender-height interaction was used to relate the measurements of 10,251 white children to particulate pollution. A 52 nmole/$m^3$ difference in annual mean particle strong acidity was associated with a 3.5% deficit in adjusted FVC and a 3.1% deficit in adjusted $FEV_1$. The deficit was larger (but not statistically larger) in lifelong residents of their communities. Deficits were also found in PEFR and $FEF_{25-75\%}$. Ratios of FEV and FVC were not statistically significant. Slightly smaller deficits were seen using total sulfate, $PM_{2.1}$, and $PM_{10}$ as pollutant exposure measures, with these deficits also being statistically significant, i.e. for FVC, $SO_4^2$ -3.06% (-4.5, -1.60); $PM_{2.1}$ -3.21% (-4.98, -1.41); $PM_{10}$ -2.42 (-4.30, -0.51). The data did not allow for clear separation of effects of the various PM exposure indicators.

***Studies of Adults***

Chestnut et al. (1991) analyzed pulmonary function data from the NHANES survey conducted from 1971 to 1974 on the non-institutionalized U.S. population aged 1 to 74. The analysis was restricted to 49 urban sampling units where TSP measurements were available. A subsample of 6,913 adults (aged 25 to 74) were given spirometric tests using an Ohio Medical Instrument Corporation Model 800 electronic spirometer. Endpoints included FVC, $FEV_{1.0}$, and MMEF. The U.S. EPA's SAROAD data base was used to obtain data from population oriented air monitors in the 49 areas. Average TSP concentrations for previous years were used as the exposure measure. All individuals with reproducible results were included in a multiple regression analysis that included terms for age, height, gender, ethnic group, obesity, and TSP. Both a nonparametric analysis and a regression analysis suggested that TSP was associated with decreased FVC at TSP levels greater than 60 $\mu$g/$m^3$.

Tashkin et al. (1994) reported on the results of a long term lung function study of adults living in three areas of southern California. The areas were (1) Lancaster, with moderate levels of photochemical oxidants and low levels of other pollutants, (2) Glendora, with very high levels of photochemical oxidants, sulfates, and particulate matter, and (3) Long Beach, with high levels of sulfates and oxides of nitrogen. A mobile lung function laboratory was used to gather pulmonary function measurements and collect information on a modified NHLBI questionnaire. Residents of each area were tested twice over a 5 or 6-year interval, but during the same month each time.

The testing schedule was as follows: (1) Lancaster, 1973 to 1974 and 1978 to 1979; (2) Glendora, 1977 to 1978 and 1982 1983; and (3) Long Beach, 1974 1975 and 1980 to 1982. Significantly larger annual decreases in $FEV_{1.0}$ were found in both Long Beach and Glendora as compared with Lancaster. These results were consistent across gender, and were adjusted for age, height, smoking status, and allergies. The decrease was largest in Long Beach, but only slightly larger than in Glendora. Smoking showed a larger effect than did area of residence. No clear attribution of observed effects to one or the other of PM, $NO_2$, or photochemical oxidants was possible.

Ackermann-Liebrich et al. (1996) studied the effects of long term exposure to air pollutants on lung function in adults. A sample of 9651 subjects aged 18 to 60 were studied in eight different areas of Switzerland. FVC and $FEV_1$ were regressed against the natural logarithms of height, weight, age, age squared, gender, educational level, nationality, and work place exposure. Results were reported separately for never smokers and smokers. The results suggested that a 10 $\mu g/m^3$ increase in annual average $PM_{10}$ was associated with a 3.4 percent decrease in FVC for healthy never smokers. Results were also consistent and significant for $NO_2$ and $SO_2$, but less so for $O_3$.

Xu et al. (1991) studied lung function in adults in areas of Beijing, China in 1986. A stratified sampling plan over three areas with historically different pollution was used. A trained interviewer obtained information on history of chest illness, respiratory symptoms, cigarette smoking, occupational exposure, residential history, educational level, and type of fuel used for cooking. Pulmonary function measurements were made according to guidelines of the American Thoracic Society. Outdoor particulate matter (TSP) and $SO_2$ were obtained for 1981 to 1985 from stations included in the World Health Organization Global Air Monitoring Programs. Multiple linear regression was used to assess the impact of air pollution on $FEV_{1.0}$ and FVC. Highly significant decreases in $FEV_{1.0}$ and FVC as a function of log($SO_2$) and log(TSP) were found.

***Chronic Pulmonary Function Studies Summary***

The chronic pulmonary function studies (Table 12-22) are less numerous than the acute exposure studies. The Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) studies

had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect for children from particulate pollution indexed by TSP, $PM_{15}$, $PM_{2.5}$ or sulfates. On the other hand, Spektor et al. (1991) reported a decrease in PEFR in Brazilian children related to $PM_{10}$ based on limited data from summer and winter of one year. Also, the latest study of Raizenne et al. (1996) found significant associations of effects on $FEV_1$ or FVC in U.S. and Canadian children with both acidic particles and other PM indicators. As for adults, Chestnut et al. (1991) reported that an increase in TSP was associated with a decline in FVC, and Ackermann-Liebrich et al. (1996) found a small but significant decrease in FVC related to $PM_{10}$ in healthy adult non-smokers. Also, Xu et al. (1991) reported decrements in $FEV_{1.0}$ and FVC as a function of log ($SO_2$) and log (TSP). Overall, the available studies provide only very limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, $PM_{10}$, sulfates, etc.). However, it should be noted that cross sectional studies require very large sample sizes to detect differences because the studies cannot eliminate person to person variation which is much larger than the within person variation. Thus, the lack of statistical significance cannot be taken as proof of no effect.

## 12.5 HUMAN HEALTH EFFECTS ASSOCIATED WITH ACID AEROSOL EXPOSURE

One key consideration in the evaluation of PM-health effects is: Are there specific chemical components of PM capable of being responsible for some or all of the noted associations between PM and human health? The presence of known toxic constituents within ambient particles would add to the plausibility of these associations. Since the time of the London Fog of 1952 and other major pollution episodes earlier in this century, the acidity of aerosols is one characteristic suspected of contributing to health effects by PM air

## TABLE 12-22. STUDIES OF LONG-TERM PARTICULATE MATTER EFFECTS ON PULMONARY FUNCTION

| Study | PM Type & No. Sites | PM Mean & Range | Model Type | Other pollutants measured | Weather & Other Factors | Pollutants in model | Decrease* (Confidence Interval) |
|---|---|---|---|---|---|---|---|
| Ware et al. (1986) Study of lung function in children in 6 U.S. cities Survey done 1974-1977 | Daily monitoring of TSP, $SO_2$, $NO_2$, and $O_3$ at each city | City TSP means ranged from 39 to 114 $\mu g/m^3$ | Linear regression using logarithm of PFT value | $SO_2$, $NO_2$ | City, gender, parental education, history of asthma, age, height, weight | | Non-significant changes of .06% (-.27, .39) for first round and -.09% (-.42, .24) for second round |
| Dockery et al. (1989) Study of lung function in children in 6 cities in the U.S. Survey done 1980-1981 | Daily monitoring of $PM_{15}$, sulfate fraction at each city | City $PM_{15}$ means ranged from 20 to 59 $\mu g/m^3$ | Linear regression using logarithm of PFT value | $SO_2$, $NO_2$ | City, gender, parental education, history of asthma, age, height, weight | | No significant relationship found with $PM_{10}$ |
| Neas et al. (1994) Study of lung function in children in 6 cities in the U.S. Data collected from 1983-1988. | Daily monitoring of $PM_{2.5}$ and sulfate fraction at each city | Not given | Linear regression using logarithm of PFT value | $SO_2$, $NO_2$, and $O_3$ | City, gender, parental education, history of asthma, age, height, weight | $PM_{2.5}$ | FVC and $FEV_1$ not changed. Values could not be converted to mls. |
| Raizenne et al. (1996) Study of lung function in children aged 8 to 12 in 22 communities in the U.S. and Canada. | 24 hour samples of particle strong acidity at 22 sites, as well as $PM_{2.1}$, $PM_{10}$, and sulfates | Not given | Two step linear regression using natural logarithm of lung function | ozone | Age, weight, height, gender, and gender by height interaction | All PM measures separately | Decreases in FVC and $FEV_1$ were about 2 to 3.5 percent over the range of the pollution measures. |

**TABLE 12-22 (cont'd). STUDIES OF LONG-TERM PARTICULATE MATTER EFFECTS ON PULMONARY FUNCTION**

| Study | PM Type & No. Sites | PM Mean & Range | Model type | Other pollutants measured | Weather & Other Factors | Pollutants in model | Decrease* (Confidence Interval) |
|---|---|---|---|---|---|---|---|
| Spector et al. (1991) Study of lung function in school-age children in Cubatao, Brazil. Lung function measured in the summer and winter of 1988. | 12 hour samples of $PM_2$ and $PM_{10}$ were collected at 6 sites from March to November, 1988. | $PM_{10}$ ave. annual means ranged from 43 to 140 $\mu g/m^3$ | Linear regression using previous months ave. $PM_{10}$ at the local site | $SO_2$ and ozone | not given | PM$_{10}$ | Decreases in $FEV_1$ averaged about 2.5 mL/($\mu g/m^3$) per 50 $\mu g/m^3$ $PM_{10}$. |
| Ackermann-Liebrich et al. (1996), study of 9,651 adults in 8 areas of Switzerland done in 1991 | Continuous measurements of $SO_2$, $NO_2$, TSP, $O_3$, and $PM_{10}$ | $PM_{10}$ in 1993 ranged from 10.1 to 33.4; mean 21.2 | Linear regression using logarithm of PFT value | TSP, $SO_2$, $NO_2$, $O_3$ | Height, weight, age, gender, atopic status | | Significant 3.4% decrease in FVC and 1.6% FEV1 decrease related to $PM_{10}$ in healthy non-smokers. Similar results found for non- and former smokers. |

*Decreases in lung function calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in $PM_{10}$ or 100 $\mu g/m^3$ increase in TSP.

pollution. Though certainly not the only PM component with potentially toxic effects, acidic aerosols have received more epidemiologic study than have other PM components, to date.

Several epidemiologic studies have directly examined the health effects associated with ambient particulate strong acid aerosol ($H^+$) exposures. The historical scarcity of such analyses was due in large part to the absence of adequate ambient acid measurement techniques in the past and to the lack of routine acid aerosol monitoring in more recent years. However, studies now exist that allow an assessment as to whether human health effects may be associated with exposures to ambient acid aerosols, both: (1) as derived from reexamination of older, historically important data on air pollution episode events in North America and Europe, and; (2) as can be deduced from more recent epidemiology studies carried out in the U.S., Canada, and Europe. This section concisely reviews these studies, first as they relate to acute exposure effects, and then as they pertain to chronic exposure effects. Because of the relative scarcity of direct acid aerosol measurements until recent years, part of this section is also devoted to identifying studies of situations in which there is good reason to suspect that high ambient acid concentrations existed in the evaluated study areas. From all of these studies, the nature of any observed health associations are summarized as a basis for drawing health effects conclusions, and for suggesting directions for future research. The material in this review was based upon the acid aerosols issue paper prepared by the U.S. Environmental Protection Agency (1989), as well as more recent evidence, as appropriate.

### 12.5.1 Evidence Evaluating the Relationship between Acid Aerosols and Health Effects During Pollution Episodes

Some of the earliest indications of associations between ambient air acid aerosols and human health effects can be discerned upon reexamination of historically important air pollution episode events. These include, for example, the Meuse Valley (Belgium), Donora, PA (USA), and well-known London (UK) episodes, as discussed below.

#### 12.5.1.1 Meuse Valley

Firket (1931) described morbidity and mortality related to the fogs of December 1930 in the Meuse Valley of Belgium. A detailed discussion of health effects causes was presented, and he concluded that, while multiple pollutants existed in this atmosphere, the main component of the fog that caused the observed health effects was sulfuric acid. This conclusion was based both upon consideration of the emissions in the valley, the weather conditions and the aerometric chemistry required for the production of sulfuric acid. Additionally, the pathophysiology seen was thought to relate to sulfuric acid exposure more so than to other possible agents. More than 60 persons died from this acid fog and several hundred suffered respiratory problems, with a large number becoming complicated with cardiovascular insufficiency. The mortality rate during the fog was over ten times higher than the normal rate. Those persons especially affected by the fog were the elderly, those suffering from asthma, heart patients, and other debilitated individuals. Most children were not allowed outside during the fog and few attended school. Unfortunately, no actual measurements of acid aerosols in ambient air during the episode are available by which to establish clearly their role in producing the observed health effects versus the relative contributions of other specific pollutants.

#### 12.5.1.2 Donora

Schrenk et al. (1949) reported on atmospheric pollutant exposures and the health effects of the smog episode of October 1948 in Donora, PA. A total of 5,910 persons (or 42.7 percent) of the total population of Donora experienced some effect from the smog. The air pollutant-laden fog lasted from the 28th to the 30th of October, and during a 2-week period 20 deaths took place, 18 of them being attributed to the fog. An extensive investigation by the U.S. Public Health Service concluded that the health effects observed were mainly due to an irritation of the respiratory tract. Mild upper respiratory tract symptoms were evenly distributed through all age groups and, on the average, were of less than four days duration. Cough was the most predominant symptom; it occurred in one-third of the population, and was evenly distributed through all age groups. Dyspnea was the most frequent symptom in the more severely affected, being reported by 13 percent of the population, with a steep rise as age progressed to 55 years; above this age, more than half of the persons affected complained of dyspnea.

It seems reasonable to state that, while no single substance can be clearly identified as being responsible for the October 1948 episode, the observed health effects syndrome could have likely been produced by two or more of the contaminants, i.e., $SO_2$ and its transformation products together with other PM constitutes, as among the more significant contaminants present. Hemeon (1955) examined the water soluble fraction of solids on a filter of an electronic air cleaner operating during the smog in Donora and concluded that acid salts were an important component.

#### 12.5.1.3 London Acid Aerosol Fogs

Based on the mortality rate in the Meuse Valley, Firket (1931) had estimated that 3,179 sudden deaths would likely occur if a pollutant fog similar to that in the Meuse Valley occurred in London. An estimated 4,000 deaths did later indeed occur during the London Fog of December 1952, as noted by Martin (1964). During that fog evidence of bronchial irritation, dyspnea, bronchospasm and, in some cases, cyanosis is clear from hospital records and from the reports of general practitioners. There was a considerable increase in sudden deaths from respiratory and cardiovascular conditions. The nature of these sudden deaths remains a matter for speculation since no specific cause was found at autopsy. Evidence of irritation of the respiratory tract was, however, frequently found and it is not unreasonable to suppose that acute anoxia due either to bronchospasm or exudate in the respiratory tract was an important factor. Also, the United Kingdom Ministry of Health (1954) report on this fog stated that, in the presence of moisture, aided perhaps by the surface activity of minute solid particles in fog, some sulfur dioxide is oxidized to trioxide. The report concluded that: "It is probable, therefore, that sulfur trioxide dissolved as sulfuric acid in fog droplets, appreciably reinforced the harmful effects."

Martin and Bradley (1960) reported increases in daily total mortality among the elderly and persons with preexisting respiratory or cardiac disease in relation to $SO_2$ and PM (measured as British Smoke; BS) levels in London during fog episodes in the winter of 1958 to 1959. The pathological findings in 12 fatal cases and the clinical evidence of practitioners seem to indicate clearly that the harmful effects of the fog were produced by the irritating action of polluted air drawn into the lungs. These effects were more obvious in people who already suffered from a chronic respiratory disease and whose bronchi were presumably more liable to bronchospasm.

Waller (1963) reported that sulfuric acid was one of the pollutants considered as a possible cause of the increased morbidity and mortality noted during the London fog of December 1952. As noted earlier, following the 1952 pollution episode daily measurements of BS and $SO_2$ made in London starting in 1954. Concentrations of sulfuric acid, calculated from net aerosol acidity, were also measured during air pollution episodes and, later, on a daily basis, starting in 1963. All of these historical acid measurements must be viewed with caution, since filter artifact formation is possible for these samples. For example, there was no attempt to protect the sample filters from ambient $SO_2$ or $NH_3$, which could result in excess acid formation or in acid neutralization, respectively, on the samples. No regular measurements of sulfuric acid were made during the winter of 1955 to 1956, but some was detected at times of high pollution. For example, Waller and Lawther (1957) detected the presence of acid droplets in samples collected in January of 1956. Insufficient measurements were made, however, during the rest of the winter of 1955 to 1956 to study the effects of the acid aerosol present. Waller (1963) later reported measuring acid droplets in London in the winter of 1958 to 1959 with mass median diameter of 0.5 μm. Commins (1963) measured particulate acid in the city of London and found concentrations especially high at times of fog reaching $H^+$ levels of 678 $\mu g/m^3$ of air (calculated as sulfuric acid). Typical winter daily concentrations were 18 $\mu g/m^3$ compared to 7 $\mu g/m^3$ in the summer. The sulfuric acid content of the air in the city of London at the time could range up to 10 percent of the total sulfur.

Acid aerosol data collected by Commins and Waller (1967) during the December 1962 London Fog episode, which occurred almost exactly 10 years after the 1952 episode, provide some of the strongest evidence that acid aerosols were elevated during the 1950's episodes. As shown in Figure 12-10, 24 h average acid concentrations reached 378 $\mu g/m^3$ (as $H_2SO_4$) on the peak mortality day during this later, less severe, London episode. Both BS and $SO_2$ were similarly elevated on these episode days, however, so it is not possible to identify

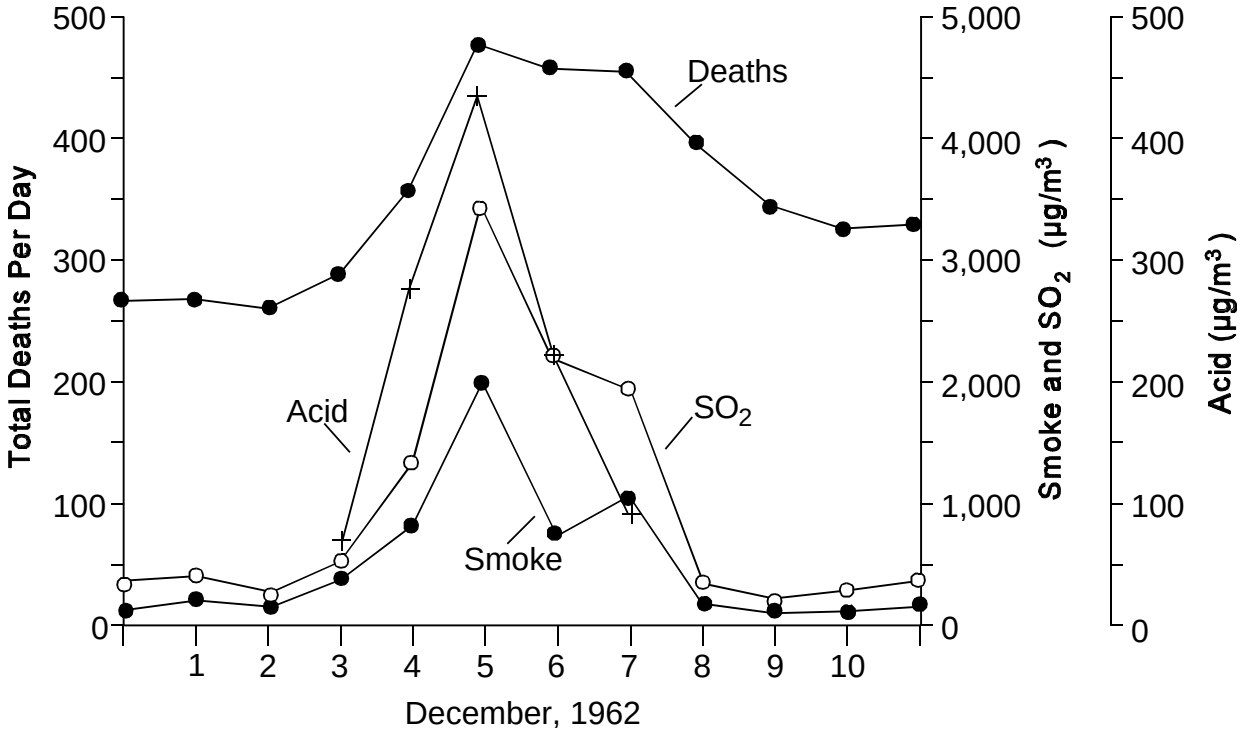


**Figure 12-10. December 1962, London pollution episode.**

Source: Adapted from Ito (1990).

$H_2SO_4$ as the sole causal pollutant. Not all of the measured acids during fog episodes would necessarily be respirable, reducing their health effects from that implied by the total $H_2SO_4$ concentration. However, these $H^+$ data from the 1962 episode do support past anecdotal evidence that elevated strong acid concentrations were present during the major London Fog pollution episodes.

Lawther et al. (1970) reported an association between daily pollutant levels (BS and $SO_2$) and worsening of health status among a group of over 1,000 chronic bronchitis patients in London during the winters of 1959 to 1960 and 1964 to 1965. A daily technique for self-assessment of day-to-day change in health status was used. The concentration of acid aerosol rose with that of smoke, and it is likely to have been partly responsible for health effects observed in these chronic bronchitic patients. Since many patients' symptoms become worse even at times of relatively low humidity, this suggests that small droplets of strong acid had more effect than larger ones. An

interesting study was also conducted on a smaller sample of the patients during in the winters of 1964 to 1965 and 1967 to 1968 when pollutant levels were somewhat lower than in earlier years. Approximately 50 subjects selected for their susceptibility to air pollutant effects formed the cohort. Daily apparent sulfuric acid, measured at St. Bartholomew Hospital Medical College, was reported as having a relatively high correlation with health effects in the 1964 to 1965 winter. For 1967 to 1968, all these correlation coefficients were lower, but still significant. The authors comment that the patients selected must have been particularly sensitive to pollution, since from past experience no correlation would have been expected with such very low levels of pollution encountered by such a small group.

The studies discussed above suggest that mortality and morbidity effects can be associated with pollutant mixes which included elevated levels of ambient air concentrations of acid aerosols. The calculations and measurements of sulfuric acid levels (estimated to range up to 378 (24-h) or 678 $\mu g/m^3$ (1-h) during some London episodes in the late fifties and early sixties provide a plausible basis for hypothesizing contributions of sulfuric acid aerosols to the health effects observed during those episodes.

## 12.5.2 Quantitative Analysis of Earlier Acid Aerosol Studies

### 12.5.2.1 London Acute Mortality and Daily Acid Aerosol Measurements

Thurston et al. (1989) conducted a reanalysis of the London mortality data for a multi-year period in which daily direct acid aerosol measurements were made at St. Bartholomew's Medical College. The data considered in this analysis include pollution and mortality records collected in Greater London during winter periods (November 1 to February 29) beginning in November 1963 and ending in February 1972. The air pollution data were compiled from one of two sources. First, BS and $SO_2$ data (as reported in $\mu g/m^3$) were compiled as daily means of seven sites run by the London County Council and spatially distributed throughout London County. A second data set of BS, $SO_2$ and aerosol acidity (calculated as $\mu g/m^3$ sulfuric acid) was also compiled for one central London site run by the Medical Research Council Air Pollution Research unit at the St. Bartholomew's Medical College. The Greater London mortality data were obtained from the London General Register Office for winter periods (November to February) beginning in 1958, and for all days commencing in April 1965. Total mortality, respiratory mortality, and

cardiovascular mortality were all compiled daily during these periods, but only total mortality was considered in this work. The Greater London population was fairly stable during the period considered in this research (1963 to 1972), averaging about 8 million people. The pollution and mortality data for each of the nine winters of data were combined into one data set for analysis. This is reasonable in this case because the period under study, late 1963 to early 1972, is subsequent to the implementation of the London smoke control zones (1961 to 1963), and is therefore a period of fairly constant average winter pollutant concentrations. Prior to combining the data, each year's total mortality data were also prefiltered using a high-pass filter that weights the mortality data in a manner very similar to the calculation of deviations from a 15-day moving average of mortality, except that it eliminates the undesirable long-term cyclical fluctuations. Although the filtered total mortality has largely removed slow moving fluctuations in the mortality data, the winters of 1967 to 1968 and 1969 to 1970 were still slightly nonstationary, probably due to influenza epidemics in those years. It may have been desirable to also control for these remaining effects by considering an influenza epidemic dummy variable in subsequent regression analyses of these data. The resulting data set comprised a total of 921 observations of daily pollution, total mortality, and filtered total mortality data for the nine-winter data set.

In the Thurston et al. (1989) results, the log of $H_2SO_4$ measured at the central site was much more strongly correlated with raw total daily mortality than any measure of BS or $SO_2$ especially when it was correlated with the next day mortality ($r = 0.31$). It is also clear that the logarithm transformation enhances the acid-mortality association more than is true for BS or $SO_2$. For the filtered mortality variable, however, the $H_2SO_4$ correlation with next day filtered mortality (e.g., $r = 0.19$ for log ($H_2SO_4$) was weakened versus that for raw total mortality. Thus, the St. Bartholomew's College $H_2SO_4$ measurements appear to be correlated with Greater London mortality, especially before the mortality data are filtered for slow moving fluctuations. Mortality-pollution crosscorrelation analyses indicated that mortality effects usually followed pollution in time even after filtering both series (Thurston et al., 1989), a basic consideration in inferring casual association.

The superiority of the log of $H_2SO_4$ concentration versus the raw $H_2SO_4$ data in correlations with total mortality agrees with the previous analyses of British Smoke-total mortality associations. This may imply that a "saturation" of mortality effects is indeed occurring over two

or more days, and that a cumulative effect of several episode days may be more relevant than modeling a single day effect alone. This may be due to avertive behavior, especially since episode warnings were publicized at the time of high pollution. Most likely, however, the "saturation" of effects is due to the premature death of the most susceptible people on prior moderate pollution days.

A more extensive analysis of the London total mortality and acid aerosol data was conducted by Ito et al. (1993) for 1965 to 1972, when daily acid measurements were available year-round and the air pollution levels were non-episodic (see Figure 12-11). BS, $SO_2$, $H_2SO_4$, and weather variables (temperature and humidity) were examined for their short-term associations with daily mortality after removal of long-term components from each series via prewhitening, in order to obtain "rational" crosscorrelations. Power spectra of the variance of mortality, pollution, and temperature variables were employed in the development of this model. Also, first order autocorrelations were found to be significant, and were evaluated. Significant associations with same day and following days' mortality were found for all three pollutants considered. In the most extensively controlled model, the winter mean pollutant effect was estimated to range from 2 to 3% of the mean 278 deaths/day total mortality, but all three pollutants gave similar results (for mean $H_2SO_4$ = 5.0 $\mu g/m^3$, $SO_2$ = 293 $\mu g/m^3$, or BS = 72 $\mu g/m^3$) and their respective effects could not be separated, due to their high intercorrelation. These models were fit to the (separate) 1962 London acid/mortality episode data and found to fit well, supporting the validity of such deviation-derived mortality estimates.

Lippmann and Ito (1995) conducted a preliminary graphically-based analysis of the year-round 1965 to 1972 London pollution and mortality data set that controlled for same-day temperature effects by analyzing restricted temperature ranges in each season. This was done to provide an alternative to more empirical approaches applied to these data in prior analyses. In each season, the majority of days fell within one or two temperature ranges, within which the mortality also fell within narrow ranges. Within these restricted ranges,

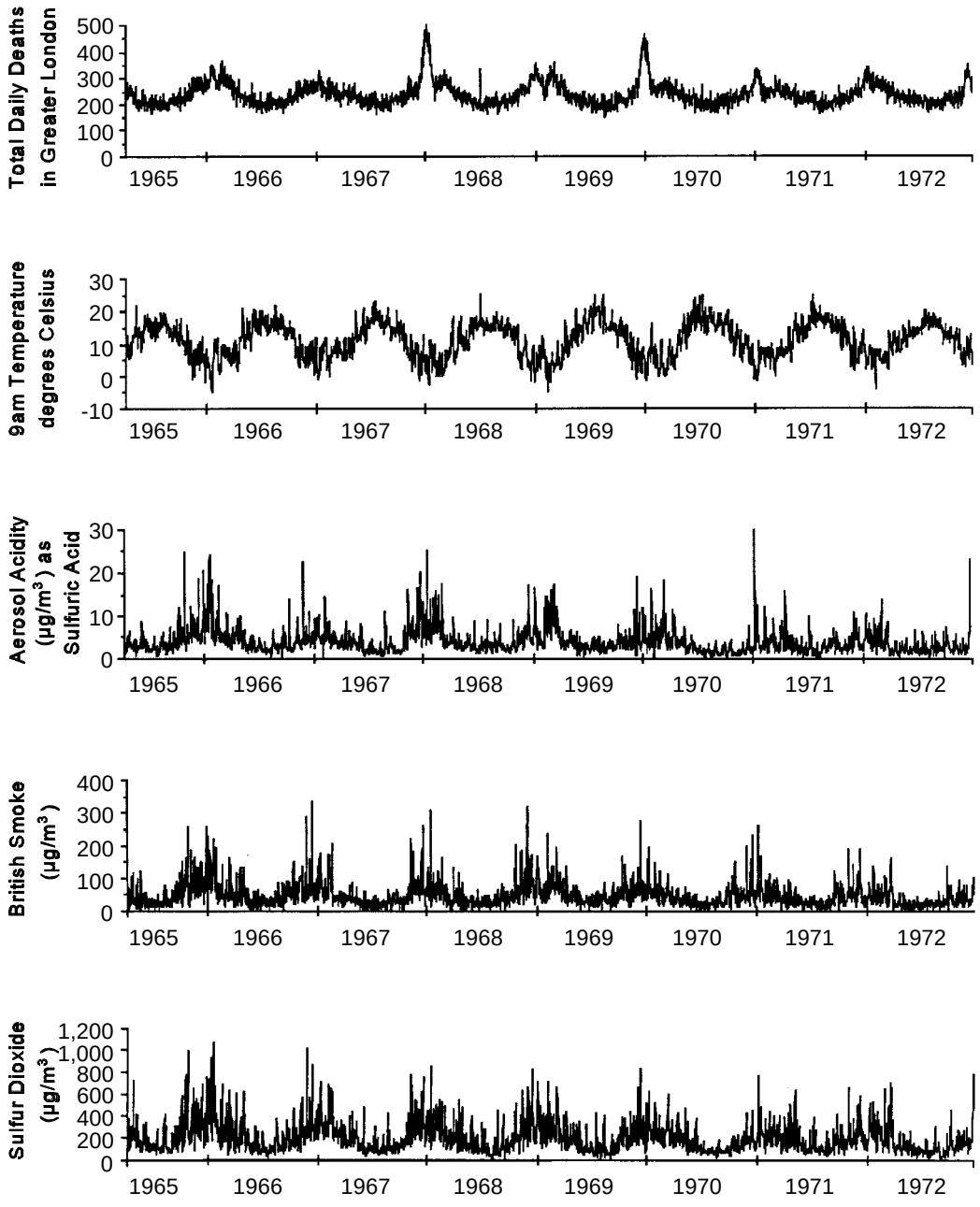


**Figure 12-11. Time series plots of daily mortality, pollution, and temperature in London, England, 1965 to 1972 (Ito et al., 1993).**

analyses indicated that there were relatively strong associations between daily mortality and the daily logs of the concentrations of $H^+$ and $SO_2$. By contrast, the mortality association with BS was much weaker, especially in the winter and summer. The authors indicate that more comprehensive analyses are needed, but assert that such analyses provide a useful complement to model-based approaches. Things as yet not addressed by this analysis include the need to control for the potential effects of prior days' extreme temperatures (i.e., lagged effects), which are known to be important in winter, and the direct addressing of potential temperature effects within the ranges considered. Probably the most interesting result of these analyses is that the $H^+$-mortality association is found even in the summertime, when the daily $H^+$ concentrations do not exceed approximately 10 μg/$m^3$, as $H_2SO_4$ (~ 200 nmoles $H^+$/ $m^3$), which are concentrations not unlike those presently experienced during the summer in the eastern United States.

These recent analyses by Thurston et al. (1989) and by Ito et al. (1993) of daily direct acid aerosol measurements over a long span of time (1963 to 1972) in London are especially important in providing more data to examine for associations between acute exposures to ambient acid aerosols and mortality at $H^+$ levels more relevant to those presently seen in North America. Also, the work of Lippmann and Ito (1995) indicates that this acute $H^+$-mortality association can exist at concentrations below 200 nmoles/$m^3$ $H^+$, and under summertime conditions.

### 12.5.3 Studies Relating Acute Health Effects to Sulfates

Sulfate species usually represent the principal component of particulate strong acid aerosols (primarily as $H_2SO_4$ or $NH_4HSO_4$). As a result, variations in measured sulfate levels have been found to represent a reasonably reliable surrogate for variations in strong particulate acid aerosol levels over time at a site (Lippmann and Thurston, 1995). However, sulfates are not necessarily as useful for intercomparing aerosol particulate acidity levels between sites. This is because measurements of total sulfate levels comprise not only strongly acidic sulfates, but, in fact, are usually dominated by sulfates that are only weakly acidic (e.g., $(NH_4)_2SO_4$). Moreover, it has been found that local ammonia levels can diminish the ambient $H^+/SO_4^=$ ratio experienced at a site by neutralizing the strongly acidic sulfates (Suh et al., 1995). For this reason, two sites located in differing environs (e.g., urban versus suburban) may have similar $SO_4^=$ levels but different $H^+/SO_4^=$ ratios, merely because the population density around the two sites is different (Ozkaynak et al.,

1994). Therefore, cross-sectional studies using sulfates may be limited in the insight they may provide into the potential health effects of acid aerosol exposures, especially if they compare sites with differing surrounding land uses. However, if two monitoring sites are in the same airshed, they will usually still be highly correlated over time, as their particulate $H^+$ concentrations will rise and fall together from day to day as regional sulfate levels rise and fall (e.g., see Thurston et al. 1994a). The surrounding land use dependence of the $H^+/SO_4^=$ ratio may limit somewhat the usefulness of sulfates as an index of $H^+$ differences between sites but may not adversely affect time series studies using sulfate data as an index of particulate aerosol strong acidity.

#### 12.5.3.1 Canadian Hospital Admissions Related to Sulfate Acute Exposure Studies

Bates and Sizto (1983, 1986) reported results of an ongoing correlational study relating hospital admissions in southern Ontario to air pollutant levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The 1986 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and $SO_2$ or COH in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory (both asthma and non-asthma) admissions in summer and sulfate and ozone concentrations, but not to summer COH levels. However, Bates and Sizto noted that the data analyses were complicated by long-term trends in respiratory disease admissions unlikely related to air pollution. They nevertheless hypothesized that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer, but not in the winter.

Bates and Sizto (1987) later studied admissions to all 79 acute-care hospitals in Southern Ontario, Canada (i.e., the whole catchment area of 5.9 million people) for the months of January, February, July and August for 1974 and for 1976 to 1983. Means of the hourly maxima for $O_3$, $NO_3$, $SO_2$, coefficient of haze (COH), and aerosol sulfates were obtained from 17 stations between Windsor and Peterborough. Sulfates were measured every sixth day. Total admissions and total respiratory admissions declined about 15 percent over the course of the study period, but asthma admissions appeared to have risen. Evaluating the asthma category of admissions is complicated by the effects of a change in International Classification of Disease (ICD) coding in 1979. The analyses demonstrated that there was a consistent summertime relationship between

respiratory admissions (with or without asthma) and sulfates, ozone, and temperature. This conclusion was strengthened by the continuing lack of any association of these variables with non-respiratory conditions. The 1987 paper raised the question of whether the association of increased respiratory admissions in the summer in this region could be associated with ozone or sulfates. It was aerosol sulfates that, in summertime, explained the highest percentage of the variance in respiratory admissions; yet these were not correlated with respiratory admissions in the winter. In view of this, the authors hypothesized that the observed health effects might be attributable neither to ozone nor to sulfates, but to some other air pollutant species that "travel" with them over the region in the summer (but not in the winter).

Bates and Sizto (1987) noted that recent observations suggested the presence of peaks of $H^+$ aerosol of small particle size in this region of Canada in the summer, concomitant with elevated $O_3$ and $SO_4^=$ levels. On two days in July 1986 in eastern Toronto when ozone and sulfate levels were elevated, but not higher than on other days, peaks of $H^+$ acid aerosol lasting for up to 2 h were recorded at levels of 10 to 15 $\mu g/m^3$. The particle size was small (about 0.2 µm). Similar observations were recorded on the same days by another $H^+$ air sample operation southwest of Toronto. They raised the possibility that the types of health effects noted above might be attributable neither to ozone, nor to sulfates, but rather perhaps to acid aerosols. Thus, the evidence from Bates and Sizto (1983, 1986, 1987, 1989) neither conclusively relates sulfates nor ozone to hospital admissions. Instead, the authors conclude that the results suggest that some other pollutant(s) may be responsible, i.e., the strongly acidic summer haze that has since been measured in the region.

Lipfert and Hammerstrom (1992) reanalyzed the Bates and Sizto (1989) hospital admissions dataset for 79 acute-care hospitals in southern Ontario, incorporating more elaborate statistical methods and extending the dataset through 1985. Pollutants considered included $SO_2$, $NO_2$, $O_3$, $SO_4^=$, COH, and TSP. Long-wave influences were reduced by using the short study periods previously employed by Bates and Sizto (e.g., July and August only for summer), as well as by employing very conservative prewhitening procedures to the data. Day of week effects were also controlled. In addition, the models were more extensively specified, including a variety of new meteorological variables such as wind speed (correlated at r=-0.5 with COH). Despite this possible model overspecification, however, summerhaze pollutants (i.e., $O_3$, $SO_4^=$, and $SO_2$) were

found to have significant associations with hospital admissions in southern Ontario. In contrast, pollution associations with hospital admissions for accidental causes were nonsignificant in these models. While air pollution concentrations were generally within U.S. standards, the pollutant mean effect accounted for 19 to 24% of all summer respiratory admissions (mean admissions 40/day, mean $SO_4^=$ 11 µg/$m^3$), although the "responsible" summertime haze pollutant(s) could not be discerned by the authors with certainty.

Burnett et al. (1994) related the number of emergency or urgent daily respiratory admissions at 168 acute care hospitals in all of Ontario during 1983 to 1988 to estimates of ozone and sulfates in the vicinity of each hospital. No other pollutants were directly considered in this analysis, although the authors reported that $SO_2$ and $NO_2$ were only weakly correlated with $SO_4$ in these data (r 0.3), so these pollutants were unlikely to be confounders. Daily levels of sulfates were recorded at nine monitoring stations located throughout the province. Long-wave cycles in the admissions data were removed using a 19-day moving average equivalent high pass filter. A random effects model (wherein hospital effects were assumed to be random) was employed, using the generalized estimating equations (GEE) of Liang and Zeger (1986). After adjusting admissions data for seasonal patterns, day of week effects, and individual hospital effects, positive and statistically significant associations were found between hospital admissions and both ozone and sulfates lagged 0 to 3 days. Positive associations were found in all age groups (0 to 1, 2 to 34, 35 to 64, 65+). The bivariate relationship found between adjusted admissions and sulfates in these data are shown in Figure 12-12. In simultaneous regressions, five percent of daily respiratory admissions in the province during May to August (mean = 107.5/day) were found to be associated with $O_3$ (at 50 ppb), and one percent with $SO_4^=$ (at 5 µg/$m^3$). Positive

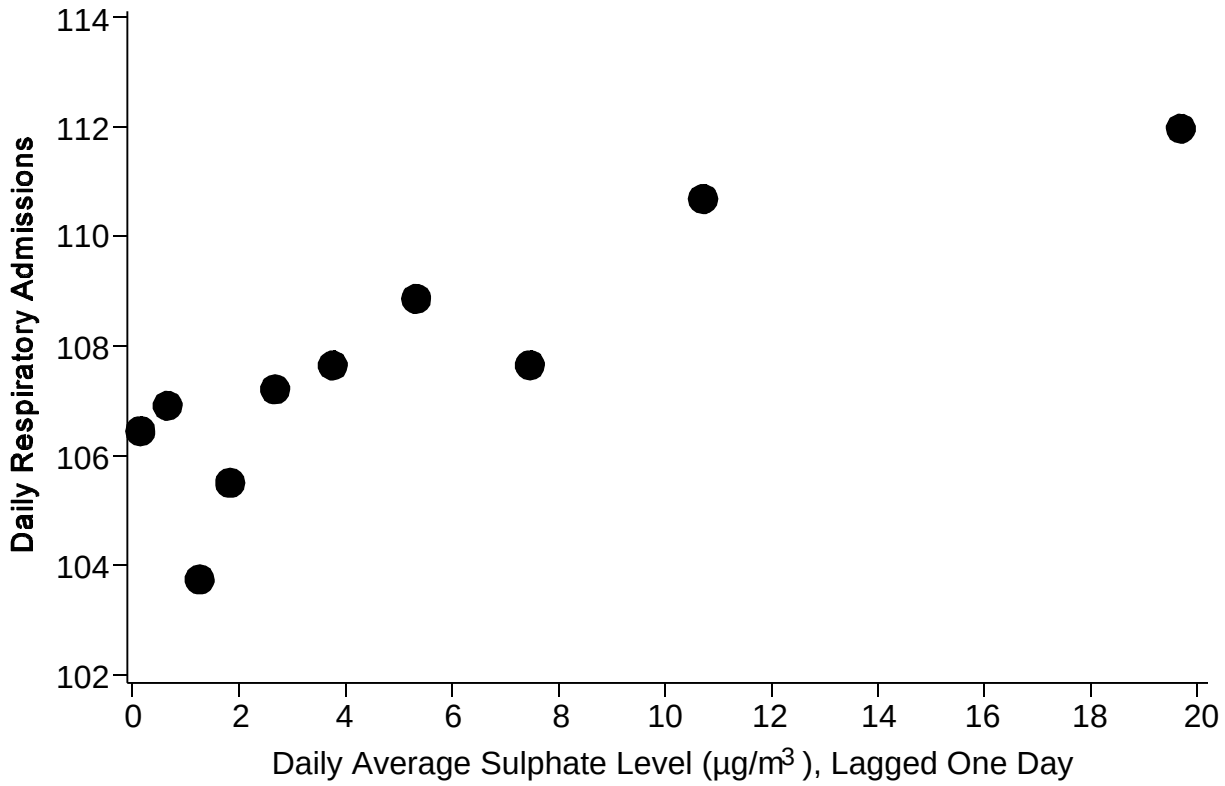


**Figure 12-12. Average number of adjusted respiratory admissions among all 168 hospitals by decile of the daily average sulfate level ($\mu$g/m$^3$), 1 day lag.**

Source: Burnett et al. (1994).

and significant air pollution associations were found for asthma, chronic obstructive pulmonary disease (COPD), and infections, but not for nonrespiratory (control) admissions, nor for respiratory admissions in the winter months (when people are indoors and levels of these pollutants are low). While these analyses employed much more sophisticated statistical methods, the results generally consistent with Bates and Sizto's prior work in this region, though ozone was found to yield a larger effect than sulfates in this study. The authors point out that $PM_{2.5}$ and $H^+$ are highly intercorrelated with sulfates in the summer months ($r > 0.8$), and that one of these agents may be responsible for the health effects relationships found with sulfates in this work. In Burnett et al. (1995), sulfate was also a predictor of hospital admissions for both respiratory and cardiac admissions, as discussed in Section 12.3.2.

#### 12.5.3.2 Other Health Effects Related to Sulfate Exposures

Ostro (1987) conducted a cross-sectional analysis of the U.S. Inhalable Particle Monitoring Network airborne particulate matter dataset, but analyzed the 1979 to 1981 annual Health Interview Surveys (HIS) to test if there were acute morbidity associations coherent with those found for mortality by Ozkaynak and Thurston (1987) during this period. Ostro reported a stronger association between several measures of morbidity (work loss days, restricted activity days, etc.) and lagged fine particle estimates than found with prior 2-week average TSP levels in 84 U.S. cities. In this analysis, a Poisson model was employed, due to the large number of zeros in the dependent variables (i.e., days with morbidity), and the analyses focused on adults aged 18 to 65. Smoking was not considered in the model, since not all metropolitan areas had data and the correlation between smoking and any of the pollutants was less than 0.03 and non-significant in the one-third of the HIS sample for which smoking data were available. This suggests that, while presumably generally important to morbidity, smoking was not a likely confounder to air pollutants in these cross-sectional analyses. Ostro concluded that his findings were consistent with the results of prior cross-sectional analyses reporting an association between mortality and exposures to fine particles and sulfates, and that "to the extent that sulfuric acid aerosols are correlated with sulfates, the results suggest that respiratory morbidity may be related to atmospheric acidity."

#### 12.5.3.3 Studies Relating Acute Health Effects to Acidic Aerosols

In recent years, a number of new studies have been conducted of acute health effects employing direct measurements of particulate strong acid aerosols. These allow a more direct test of the hypothesis that it is the $H^+$ that is responsible for the sulfates-health effects associations noted in past work.

#### 12.5.3.4 Acute Acidic Aerosol Exposure Studies of Children

Several studies have recently been carried out in the United States and Canada that examine the effects of exposures to air pollutants on pulmonary function in children at summer camps. Some of the available data derived from these studies allow evaluation of the possible involvement

of acid aerosols in the health effects observed. Furthermore, recent children's diary studies have also investigated acid aerosol effects on respiratory symptoms in the general population.

***Studies of Pulmonary Function in Children at Summer Camp***

Lippmann et al. (1983) studied 83 nonsmoking, middle class, healthy children (ages 8 to 13) during a 1980 2-week summer camp program in Indiana, PA. The children were involved in camp activities which resulted in their exercising outdoors most of the time. At least once, each child had height and weight measured and performed spirometry on an 8 liter Collins portable recording spirometer in the standing position without nose clip. During the study, peak flow rates were obtained by Mini-Wright peak flow meter at the beginning of the day or at lunch and adjusted for both age and height. Ambient air levels of TSP, hydrogen ions, and sulfates were monitored by a high-volume sampler on the rooftop of the day camp building. Ozone levels were estimated using a model that used ozone data from monitoring sites located 32 and 100 km away. The hi-volume samples were collected on $H_2SO_4$ treated quartz fiber filters for the determination of the concentration of $H^+$ and total suspended particulate matter (TSP). $H^+$ was determined from filter extract using a Gran titration. Peaks in acid concentration occurred on four days, when the acid values ranged between 4 and 6.3 $\mu g/m^3$ (if as $H_2SO_4$). On many occasions, there was no measurable $H_2SO_4$ in the atmosphere. While effects were reported as being significantly associated with exposure to ozone, no effects were found to be related to exposure to $H_2SO_4$ at the relatively low levels observed during the study.

Bock et al. (1985) and Lioy et al. (1985) examined pulmonary function of 39 children at a camp in Mendham, New Jersey during a 5-week period in July to August, 1982. Ozone was continuously monitored using chemiluminescent analysis. Ambient aerosol samples were collected on Teflon filters with a dichotomous sampler having a 15 µm fractionation inlet and a coarse/fine cut size of 2.5 µm (Sierra Model 244-E). Aerosol acidity as measured by strong acid ($H^+$) content, was determined using the pH method. Highly significant changes in peak expiratory flow rate (PEFR) were found to be related to ozone exposure, as well as a baseline shift in PEFR lasting approximately one week following a haze episode in which the $O_3$ exposure exceeded the NAAQS for four consecutive days that included a maximum concentration of 185 ppb. There was no apparent effect of $H^+$ on pulmonary function. The authors did state, however, that the

persistent effects associated with the ozone episode could have been due to acid sulfates as well as, or in addition to, ozone, but additional uncollected data were needed to evaluate this possibility.

During a 4-week period in 1984, Lioy et al. (1987) and Spektor et al. (1988) measured respiratory function of 91 active children who were residing at a summer camp on Fairview Lake in northwestern New Jersey. Continuous data were collected for ambient temperature, humidity, wind speed and direction, and concentrations of $O_3$, $H_2SO_4$, and total sulfates were determined. Ozone was measured by U.V. absorption, and $H_2SO_4$ and total sulfates were alternately determined by a flame photometric sulfate analyzer (Meloy Model 285) preceded by a programmed thermal pretreatment unit. The ambient aerosol samples were collected on quartz fiber filters with a dichotomous sampler having a 15 μm fractionating inlet ($PM_{l5}$ and a coarse/fine cut-size of 2.5 μm (Sierra Model 244-E). Aerosol acidity, as measured by strong acid ($H^+$) content, was determined using the pH method. The maximum values recorded for $H_2SO_4$ and $NH_4HSO_4$ were 4 and 20 μg/m$^3$ respectively. While effects were reported as being associated with exposure to ozone, no effects were found to be directly related to exposure to the acid aerosol concentrations experienced in this study.

Raizenne et al. (1987) reported analyses of data from a study in Ontario, Canada. In 1983, fifty two campers (23 were asthmatics) at a summer camp were studied to examine lung function performance in relation to daily pollutant concentrations. The health assessment included a pre-camp clinical evaluation, a telephone administered questionnaire on respiratory health, daily spirometry and symptoms measurements. Pollutants measured included $O_3$, respirable particles, sulfates, $NO_2$, and $SO_2$. Respirable sulfates were highly variable and ranged from 10 to 26 μg/m$^3$. Sulfate as sulfuric acid was usually very low. Raizenne et al. (1989) report that $O_3$, sulfate, and $PM_{2.5}$ were associated with decrements in lung function of children. Evidence of decrements in specific lung function indices were related to current pollution levels and to a 12 to 24 h lag function for $PM_{2.5}$, $SO_4$, $O_3$ and temperature. Although both asthmatic and non-asthmatics had similar data trends, only responses in the non-asthmatic group reached statistical significance. The authors note that all of the air pollutants were highly correlated, and thus it was not possible to apportion health effects to the individual pollutants.

Raizenne et al. (1989) studied 112 young girls who participated in one of three 2-week camp sessions at camp Kiawa, Ontario, Canada during June to August, 1986. They examined the subjects in relation to four ambient acid aerosol events (the highest $H_2SO_4$ level was 47.7 $\mu g/m^3$ during one event on July 25, 1986). The influence of air pollution on lung function was evaluated first by comparing responses on the day of a pollutant event (high acid and ozone levels) to the mean of the responses on corresponding days of low pollutant levels. For $FEV_{1.0}$ there was tendency for the lung function decrements on the event day to be greater than the response on the corresponding control days, except for the last event (when an increase in function was observed). The largest decrements for $FEV_{1.0}$ and PEFR (48 to 66 mL decline for $FEV_{1.0}$) were observed on the morning after the highest $H_2SO_4$ event, on July 25, 1986. No analyses were presented, however, that attempted to separate out pollutant effects of $H_2SO_4$ from those of $O_3$.

Airway hyper-responsiveness was assessed using a methacholine bronchial provocation test for 96 of the subjects in the Raizenne et al. (1989) study. Children with a positive response to methacholine challenge had larger decrements compared to their nonresponsive counterparts. These preliminary results do not allow definitive statements to be made on the susceptibility of methacholine sensitive subjects. However, there are indications in these data of differential lung function profiles and responses to air pollutants in children with and without airway hyper-responsiveness. Further analyses and research are indicated.

At the same camp, twelve young females (9 to 14 years old) performed pre- and post-exercise spirometry on a day of low air pollution and at the peak of an air pollution episode. Clinical interview, atopy, and methacholine airway hyper-responsiveness tests were performed at the camp on the first 2 days of the study. Seven subjects had positive responses to methacholine challenge ($^+$MC) and five did not ($^-$MC). A standardized ergonometric physical capacity test was also administered, in which minute volume, heart rates, and total work achieved were recorded. Air monitoring was performed on site and, during the episode, air pollution concentrations were: $O_3$ exceeded 130 ppb; $H_2SO_4$ exceeded 40 $\mu g/m^3$ during a 1-h period. For the entire group (N = 12), post exercise FVC and $FEV_{1.0}$ were observed to increase on the control day and decrease on the episode day. On the control day, an average 40 mL increase in FVC due to exercise was observed ($p < .05$) for the whole group, with a 71 mL increase in +MC subjects and a 17 mL increase in -MC subjects. Although not statistically significant at $P < 0.10$, the mean FVC for the

entire group was 30 ml less on the day of high pollution versus low pollution, and this difference was more pronounced in -MC (-65 mL) than +MC (-4 mL) subjects. The effect of exercise in the model was statistically significant ($p < .05$), whereas the pollution day effect was not. These results suggest that lung function responses to exercise differ in +MC and -MC subjects under field research conditions, and that the expected normal FVC response to exercise in both groups is altered during periods of elevated ambient pollution. However, no analyses were presented that directly evaluated possible acid aerosol relationships to health effects.

It is of interest to compare results obtained in this summer camp study to findings of certain controlled human exposure studies or to other epidemiology studies. For example, Spengler et al. (1989) calculated that the children in the Raizenne et al. (1989) study received an average 1-h respiratory tract dose of 1050 nmoles of $H^+$, based on a exposure model which takes into account both the concentration of exposure, and the minute ventilation rate, but not the possible mitigating effects of airway ammonia. Spengler et al. (1989) further noted that the asthmatic subjects in the human clinical studies of Utell et al. (1983) and Koenig et al. (1983) had experienced an airway dose of approximately 1,200 nmoles of $H^+$, which evoked a response at reported concentrations of 450 $\mu g/m^3$ and 100 $\mu g/m^3$ $H_2SO_4$, respectively. These calculations suggest that, because of differences in minute ventilation rates, the peak levels occurring at Camp Kiawa during an ambient acid aerosol event may have produced exposures similar to those seen in clinical studies of asthmatic subjects. It remains to be determined as to what extent comparable C x T total respiratory tract dose(s) for $H^+$ ions may be effective in producing pulmonary function decrements beyond the short exposure times employed in the controlled human exposure studies or in producing other types of effects. For example, Spektor et al. (1989) found that increasing the length of exposure to 100 $\mu g/m^3$ sulfuric acid from 1- to 2-h increased average tracheobronchial clearance half-time from 100 to 162 percent, relative to control.

Studnicka et al. (1995) conducted a study of the effects of air pollution on the lung function of three consecutive panels of children participating in a summer camp in the Austrian Alps during the summer of 1991. On-site environmental assessment consisted of 24-h measurements of $PM_{10}$, $H^+$, and $SO_4^=$, as well as continuous measurements of $O_3$, temperature, and relative humidity. Pollen counts were sampled daily using a Burkhardt spore trap. $SO_2$ and $NO_2$ data were obtained from routine monitoring stations located at the same altitude 20 to 30 km from the camp. For 47,

45, and 41 subjects, daily $FEV_1$, FVC, and peak expiratory flow were recorded. While mean levels of ambient pollutants were generally 15% higher for Panel 1, the Panel 1 $H^+$ concentrations averaged twice as high as for the other two panels. The maximum $H^+$ exposure (during Panel 1) was 84 nmol/$m^3$ (4$\mu$g/$m^3$ $H_2SO_4$ equivalent). Compared with other camp studies discussed above, peak $H^+$ exposure was of lesser concentration, but of longer duration.

For $FEV_1$, a significant decrease of -.099 ml per nmol/$m^3$ $H^+$ ($p = 0.01$) occurred during Panel 1. Exclusion of the first 5 days or excluding the maximum $H^+$ day did not significantly alter this result. The $FEV_1/H^+$ coefficient was found to be similar (-0.74 ml per nmol/$m^3$ $H^+$; $p = 0.28$) for Panel 2, but was in the opposite direction and clearly non-significant during Panel 3 (0.10 ml per nmol/$m^3$ $H^+$; $p = 0.83$). The decrease in $FEV_1$ during Panel 1 was more pronounced when the mean exposure during the previous 4 days (4-d) was used (-2.99 ml; $FEV_1$ per nmol/$m^3$ $H^+$; $p = 0.004$), suggesting greater effects from multiple-day episodes. However, it is important to note that, while $O_3$ levels were low and not significantly correlated with $FEV_1$ throughout this study, $PM_{10}$ measurements showed associations of similar strength with $FEV_1$ during Panel 1 as were found for $H^+$ ($r_{PM10\ H^+} = 0.94$). Also, in a simultaneous model of $FEV_1$ on $H^+$ with $PM_{10}$, $O_3$, and pollen in the model, the previous 4-d mean $H^+$ variable's coefficient was of similar magnitude as for the single pollutant model (though the coefficient SE did rise). This indicates that the $H^+$ association with $FEV_1$ remained, even after controlling for other potentially confounding factors. The authors conclude that a significant $FEV_1$ decrease of 200 ml was observed in children at this camp during a summer haze episode in the Austrian Alps, and the acidic PM may, therefore, be associated with transient decreases in lung function in children. However, $PM_{10}$ showed more of a relationship than did the other pollutants such as $H^+$.

***Studies of Respiratory Symptoms and Pulmonary Function in Schoolchildren***

As part of the 6-Cities study conducted by Harvard University, a cohort of approximately 1800 children in grades two through five from six U.S. cities (Watertown, MA; Kingston-Harriman, TN; St. Louis, MO; Portage, WI; Steubenville, OH, and; Topeka, KS) was enrolled in a diary study in which parents completed a bi-weekly report on each child's daily respiratory symptoms (Schwartz et al., 1994). The study extended over 4 school years (1984 to 1988), but data were collected for only one year in each city. Environmental variables measured daily at a

central site in each city included $PM_{10}$, $PM_{2.5}$, $PM_{2.5}$ sulfur, $H^+$, $H_2SO_4$, $SO_2$, $O_3$, and nephelometry (a measurement of aerosol scattering of light, which provides an index of sub-micron particle concentration). The $H_2SO_4$ data were not analyzed in this work. The reported analysis was limited to April through August in each city to reduce seasonal confounding (n = 153). Statistical analyses involved the use of ordinary logistic regression, in which the logarithm of the odds of the response rate is modeled as a linear function of covariates, followed by the application of logistic methods incorporating corrections for autocorrelation using the GEE model proposed by Liang and Zeger (1986) and Zeger and Liang (1986) for such repeated measures studies. Regressions included a temperature and a temperature squared term, as well as city-specific and day of week dummy variables and interaction terms for city-specific temperature terms. Exploratory analyses considered pollution lags of up to 14 days. Pollutants were considered individually in the regressions, and those which were significant individually were considered in multiple pollutant models.

Lower respiratory symptoms (LRS) is defined as the reporting of at least two of: cough, chest pain, phlegm, or wheeze. Analyses of daily LRS found in individual pollutant regressions that $PM_{10}$, $PM_{2.5}$, $PM_{2.5}$ sulfur (i.e., sulfates), nephelometry, $SO_2$, and $O_3$ were all significant predictors. Of all these pollutants, $PM_{2.5}$ sulfur (i.e., sulfates) and $PM_{10}$ yielded the highest levels of significance (t = 3.35 and t = 3.47, respectively), suggesting that it is the sulfur containing fine aerosol component which was driving the PM relationships found with LRS. In the overall data analysis, aerosol acidity was not significantly associated with LRS, but associations were noted for $H^+$ above 110 nmoles/$m^3$, with a relative odds ratio of LRS estimated to be greater than 2.0 at 300 nmoles/$m^3$ $H^+$ (see Figure 12-4). Similarly, the 6-City diary analysis of upper respiratory symptoms (URS, defined as any two of hoarseness, sore throat, or fever) showed no consistent association with $H^+$ until concentrations exceeded 110 nmoles/$m^3$. The exposure-dependent increase in symptoms seen across the entire range of $PM_{10}$ certainly suggests that the effect is principally related to particle mass, and not specifically to the acidic components. Acid may increase the particulate effect if it is in high enough concentrations, however. This may relate to neutralization of lower concentrations of acidic aerosols by ammonia in the breathing zone. Further investigation of any role of aerosol acidity in modulating the effects of $PM_{10}$ is needed to clarify this.

A separate analysis of upper respiratory symptoms was also conducted using similar data and methods for three of the cities only: Watertown, MA; Kingston-Harriman, TN; St. Louis, MO (Schwartz et al., 1991b). In these cities, the pollutant with the largest regression coefficient was $H_2SO_4$ , with the strongest association falling on the prior two days. Unfortunately, comparative details about other pollutants are not provided in this paper. While sketchy, these results are consistent with the hypothesis that ambient acid aerosols in general, and $H_2SO_4$ in particular, may be associated with health effects in children.

In a study of ambient air pollution and lung function in children reported by Neas et al. (1995), a sample of 83 children living in Uniontown, PA performed twice daily peak expiratory flow rate (PEFR) measurements on 3,582 child-days during the summer of 1990. Upon arising and before retiring, each child recorded the time, three PEFR measurements, and the presence of cold, cough, or wheeze symptoms. Environmental factors were monitored, including ambient temperature, $O_3$, $SO_2$, fine particle mass, $PM_{10}$, and particle strong acidity, which was measured separately during the day (8 am to 8 pm) and night. Each child's maximum PEFR for each session was expressed as the deviation from their mean PEFR over the study and adjusted to a standard of 300 liters/minute. The session-specific average deviation was then calculated across all the children. A second order autoregressive model for PEFR was developed which included a separate intercept for evening measurements, trend, temperature, and 12-h average air pollutant concentration weighted by the number of hours each child spent outdoors during the previous 12-h period. A 12-h exposure to a 125 nmole/$m_3$ increment in $H^+$ was associated with a -2.5 liters/minute deviation in the group mean PEFR (95% CI = -4.2 to -0.8) and with increased cough incidence (odds ratio, OR = 1.6; 95% CI = 1.1 to 2.4). It should be noted, however, that $H^+$ was highly correlated with sulfates (r = 0.92) and fine particles (r = 0.86). A 30 ppb increment in ozone for 12-h was associated with a similar deviation in PEFR levels (-2.8; 95% CI = -6.7 to 1.1). However, when both $O_3$ and $H^+$ were entered into the model simultaneously, the $H^+$ effect size was only slightly reduced and remained significant. Although monitored, $PM_{10}$ results were not presented for comparison. The association between PEFR and particle strong acidity was observed among the 60 children who were reported as symptomatic on the prior symptom questionnaire (-2.5; 95% CI = -4.5 to -0.5). The authors concluded that summertime occurrences

of elevated acid aerosol and particulate sulfate pollution are associated with acute declines in peak expiratory flow rates and increased incidence of cough episodes in children.

Overall, most of these camp and school children studies provide evidence indicating an acute acidic PM effect on both children's respiratory function and symptoms. However, given the usually high correlation between acidic PM and PM in these studies, it is difficult to identify these effects solely with the acid portion of PM.

### 12.5.3.5 Acute Acid Aerosol Exposure Studies of Adults

***Acute Acid Aerosol Exposures and Asthma Symptoms in Adults***

The hypothesis that human exposures to ambient $H^+$ concentrations are associated with exacerbations of pre-existing respiratory disease was tested by a recent study of asthmatic responses to airborne acid aerosols (Ostro et al., 1989, 1991). Data on daily concentrations of aerosol $H^+$, $SO_4$, $NO_3$, and FP, as well as gaseous $SO_2$ and $HNO_3$, were tested for correlation with daily symptom, medication usage, and other variables for a panel of 207 adults with moderate to severe asthma in Denver, CO between November 1987 and March 1988. However, CO and $NO_2$, potentially confounding pollutants, were not considered in the analyses. The $H^+$ concentrations ranged from 2 to 41 neq/$m^3$ (0.01 to 2.0 µg/$m^3$ of $H_2SO_4$ equivalent), and were significantly related to both the proportion of the survey respondents reporting a moderate or worse overall asthma condition, and the proportion reporting a moderate or worse cough. However, it is important to note that these concentrations are near to or below the level of detection of $H^+$, and that, of the 74 $H^+$ values used in the analysis, 47 were predicted from the observed $SO_4^=$ value on that day ($H^+$ - $SO_4^=$ correlation = 0.66), which is more accurately measured at such low levels. $PM_{2.5}$ was also highly correlated with sulfates during this study (r = 0.86). Both logit models and ordinary least squares with a log pollution term, autoregressive terms, and terms for trend, weekend, use of gas stove, and maximum daily temperature were modeled.

Of all the pollutants considered in these analyses, $H^+$ displayed the strongest associations with asthma and cough. In the first analysis, the magnitudes of effects were compared by computing elasticities, or the percent change in the health effect due to a given percent change in the pollutant. The results for asthma indicated elasticities with respect to $SO_4$, FP, and $H^+$ of 0.060, 0.055 and 0.096, respectively (Ostro et al., 1989). This indicates that a doubling of the

concentration of $H^+$ (from 8 to 16 nmoles/$m^3$) would increase the proportion reporting a moderate to severe asthma condition by 10 percent. In their follow-up report on this study, Ostro et al. (1991) examined evidence for lagged effects, and concluded that contemporaneous measures of $H^+$ concentration provided the best associations with asthma status, and that meteorological variables were not associated with the health effects reported. They also examined the effects of exposure to $H^+$, adjusting for time spent outdoors, level of activity, and penetration of acid aerosol indoors. Based on the adjusted exposures, the effect of $H^+$ on cough increased 43%, suggesting that dose-response estimates that do not incorporate behavioral factors affecting actual $H^+$ exposures may substantially underestimate the impact of the pollution. The associations of exposure adjusted $H^+$ with moderate to severe cough and with asthma status are shown in Figures 12-13 and 12-14, respectively. Although the $H^+$ concentrations on some days had to be estimated from sulfates, and potentially confounding pollutants were not considered simultaneously with $H^+$ in the model, these results allow the consideration that human exposures to present day ambient $H^+$ concentrations may be associated with exacerbations of pre-existing respiratory disease.

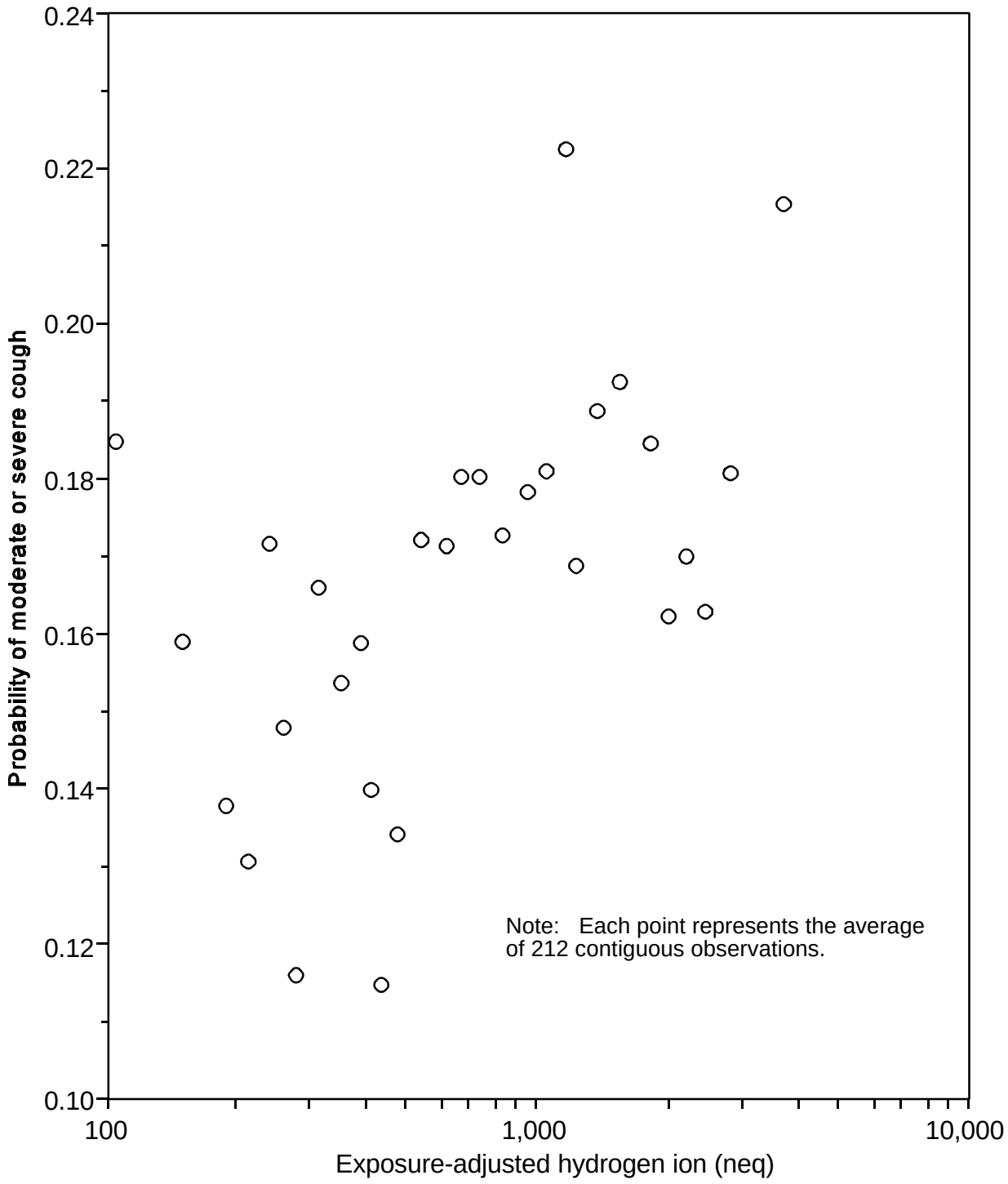


**Figure 12-13. Association of moderate or severe cough with exposure-adjusted hydrogen ion.**

Source: Ostro et al. (1991).

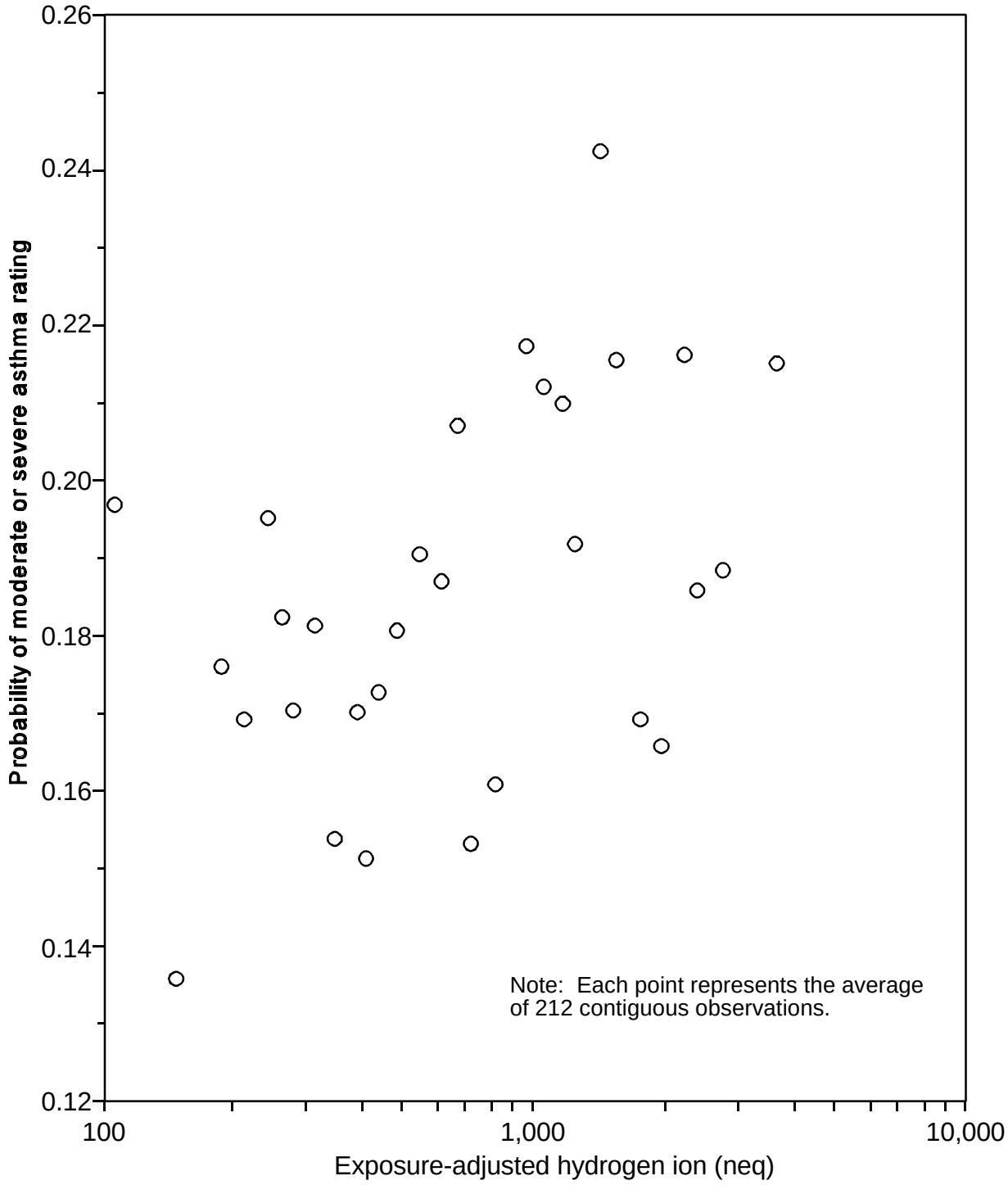


**Figure 12-14. Association of moderate or severe asthma rating with exposure-adjusted hydrogen ion.**

Source: Ostro et al. (1991).

### 12.5.3.6 Acute Acidic Aerosol Associations with Respiratory Hospital Admissions

The reported sulfate-respiratory hospital admissions associations discussed above were interpreted as potentially being due to the presence of strongly acidic aerosols on high sulfate days. Two follow-up studies of respiratory hospital admissions were conducted in New York State and in Toronto, Ontario to directly test this hypothesis.

Thurston et al. (1992) analyzed unscheduled (emergency) admissions to acute care hospitals in three New York State metropolitan areas during the summers of 1988 and 1989. Environmental variables considered included daily 1-h maximum ozone, 24-h sulfate, and particulate strong acid aerosol ($H^+$) concentrations, as well as daily maximum temperature recorded at central sites in each community. For this study, acid aerosols were sampled in residential suburbs of Buffalo, Albany, and New York City (NYC), NY. In NYC, the site was located well outside the urban core (in White Plains, 10 mi. north of the city), so the acid levels are likely to be overestimates of the levels experienced directly in the city. Comparisons between sulfates in the White Plains site and at a site in Manhattan during part of the study period showed a high correlation ($r = 0.9$), supporting the assumption that the White Plains $H^+$ data are indicative of particulate strong acid exposures in NYC. Long wave periodicities in the data were reduced by selecting a June through August study period. However, because of remaining within-season long wave cycles in the data series, they were prefiltered using sine and cosine waves with annual periodicities. Day of week effects were also controlled via regression. These adjustments resulted in non-significant autocorrelations in the data series and also improved the pollution correlations with admissions.

The strongest pollutant-respiratory admissions associations found by Thurston et al. (1992) were during the high pollution 1988 summer and in the most urbanized communities considered (i.e., Buffalo and New York City). Correlations between the pollution data and hospital admissions for non-respiratory control diseases were non-significant both before and after prefiltering. After controlling for temperature effects via simultaneous regression, the summer haze pollutants (i.e., $SO_4^=$, $H^+$, and $O_3$) remained significantly related to total respiratory and asthma admissions. However, multiple pollutant regressions were not attempted, preventing a clear discrimination of the respective effects of these pollutants. Other community pollutants (e.g., $NO_2$, $SO_2$, and CO) were not considered, but are generally low and unlikely to be highly

correlated with the studied pollutants during July and August in these cities. After filtering, $SO_4^=$ and $H^+$ were highly correlated in these cities (e.g., r = 0.86 in Buffalo, and 0.79 in NYC during the summer of 1988), supporting the contention that $SO_4$ is a useful index of $H^+$ in such time-series analyses. In regressions for the summer of 1988 for Buffalo and New York City, both $H^+$ and $SO_4^=$ had similar mean effects (3 to 4% of respiratory admissions in NYC, at mean $H^+$ = 2.4 μg/m$^3$ as $H_2SO_4$, and mean $SO_4^=$ = 9.3 $\mu$g/m$^3$; and 6 to 8% in Buffalo, at mean $H^+$ = 2.2 μg/m$^3$ as $H_2SO_4$, and mean $SO_4^=$ = 9.0 μg/m$^3$). Ozone mean effects estimates were always larger than for $H^+$ or $SO_4^=$, but the impact of the highest day was greatest for $H^+$ in all cases. This is the case in part because $H^+$ episodes are more extreme, relative to the mean, than are $O_3$ episodes (e.g., in Buffalo in 1988, the summer max./mean $H^+$ = 8.5, while the max./mean $O_3$ = 2.2). Thus, the maximum $H^+$ day in Buffalo (18.7 μg/m$^3$ as $H_2SO_4$, or 381 nmoles $H^+$/m$^3$, on August 4, 1988), was estimated to be associated with a 47% increase above the mean number of total respiratory admissions in this metropolitan area (mean = 25/day). Thus, the $H^+$ effects estimates reported in this work are dominated by the two or three peak $H^+$ days per year experienced in these cities (e.g., $H^+$ > 10 μg/m$^3$, or ~200 nmoles/m$^3$, as a 24-h average).

Thurston et al. (1994b) focused their analysis of respiratory hospital admissions in the Toronto metropolitan area during the summers (July to August) of 1986 to 1988, when they directly monitored for strong particulate acidity ($H^+$) pollution on a daily basis in that city. This study was designed specifically to test the hypothesis that the $SO_4^=$ associations found in southern Ontario by Bates and Sizto were due to $H^+$ exposures. Acid measurements were made at three sites in the Toronto metropolitan area, and were found to be highly correlated across sites (Thurston et al., 1994a). The $H^+$ data from the center city site (Breadalbane St.) were used for the health effects analyses, as there were a full 3 summers of data there (the other two sites were not operated in 1988), and because other pollutants were measured there daily, as well. The 9AM to 5PM average $H^+$ was employed in these analyses. Long wave cycles, and their associated autocorrelations, were removed by first applying an annual periodicity sine-cosine fit to the data (as well as day of week dummy variables) and analyzing the resulting residuals. Strong and significant positive associations with both asthma and respiratory admissions were found for both $O_3$ and $H^+$, and somewhat weaker significant associations with $SO_4^=$. No such associations were found for $SO_2$ or $NO_2$, nor for any pollutant with non-respiratory control admissions. Other PM

metrics examined included the mass of fine particles less than 2.5 $\mu$m in $d_a$ (FP), the mass of particles greater than 2.5 $\mu$m and less than 10 $\mu$m in $d_a$ (CP), $PM_{10}$ (= FP+CP), TSP, and non-thoracic TSP (= TSP-$PM_{10}$). Temperature was only weakly correlated with respiratory admissions, and became non-significant when entered in regressions with air pollution indices.

Simultaneous regressions and sensitivity analyses indicated that $O_3$ and $H^+$ were the summertime haze constituents of greatest importance to respiratory and asthma admissions in Toronto during these three summers. Indeed, as shown in Table 12-23, of the PM metrics considered, only $H^+$ remained significant in the respiratory admissions regression with both $O_3$ and temperature also included. The correlation of the $H^+$ and $O_3$ coefficients in this simultaneous model was non-significant (r=-0.11), indicating that these two pollutants have independent associations with respiratory admissions. As shown in Table 12-24, the 1988 results for Toronto are consistent with (i.e., not statistically different from) those found previously for nearby Buffalo, NY (approximately 100 km to the south, across Lake Ontario). As in these authors' Buffalo analysis, the maximum $H^+$ day in Toronto (August 4, 1988: $H^+$ = 391 nmoles/$m^3$) was estimated to be associated with the greatest relative risk of total respiratory and asthma admissions (1.50 and 1.53, respectively), again indicating an especially large adverse respiratory effect by summertime haze air pollutants during the few $H^+$ episode days each summer. However, a sensitivity analysis eliminating the six days having $H^+$ 100 nmoles/$m^3$ yielded a similar, and statistically significant, $H^+$ coefficient in the total respiratory admissions regression, suggesting that the association is not limited to the highest pollution days alone. The authors reviewed A.B. Hill's criteria for causality (Hill, 1965), and concluded that the associations they report between summertime haze air pollutants (i.e., $O_3$ and $H^+$) and acute exacerbations of respiratory disease (i.e., respiratory hospital admissions) are causal. It is of particular interest to note that, assuming the $H^+$ to be in the form of $NH_4HSO_4$, the "effect" per $\mu$g/$m^3$ of mass implied by these Toronto coefficients indicate that $H^+$ is six times as potent (per $\mu$g/$m^3$) as non-acidic $PM_{10}$.

**TABLE 12-23. SIMULTANEOUS REGRESSIONS OF 1986 TO 1988 TORONTO DAILY SUMMERTIME TOTAL RESPIRATORY ADMISSIONS ON TEMPERATURE AND VARIOUS POLLUTION METRICS**

| Temp, pollutant model specification | Pollutant Regression Coefficients (adm/poll unit[a]) | *P* value (one-sided) |
|---|---|---|
| | Two pollutant models | |
| T(LG0), $O_3$(LG0)[b] | 0.0503 ± 0.0205 | 0.008 |
| $H^+$(LG1) | 0.0153 ± 0.0089 | 0.044 |
| T(LG0), $O_3$(LG0) | 0.0508 ± 0.0207 | 0.008 |
| $SO_4^=$(LG1) | 0.0062 ± 0.0046 | 0.089 |
| T(LG0), $O_3$(LG0) | 0.0404 ± 0.0233 | 0.043 |
| FP(LG0) | 0.0434 ± 0.0429 | 0.157 |
| T(LG0), $O_3$(LG0) | 0.0388 ± 0.0241 | 0.055 |
| $PM_{10}$(LG0) | 0.0339 ± 0.0344 | 0.164 |
| T(LG0), $O_3$(LG0) | 0.0360 ± 0.0228 | 0.059 |
| TSP(LG0) | 0.0127 ± 0.0175 | 0.235 |

[a]Pollution units: nmole/$m^3$ for $H^+$ and $SO_4^=$; ppb for $O_3$; and $\mu g/m^3$ for FP, CP, $PM_{10}$, TSP, TSP-$PM_{10}$.
[b]LGO: zero day lag; LG1: one day lag.

Source: Thurston et al. (1994b)

These two new studies of daily respiratory hospital admissions in New York State cities and in Toronto, Ontario support the hypothesis that the summertime sulfate concentrations previously found to be correlated with respiratory admissions are indeed accompanied by acidic aerosols in Eastern North America. Furthermore, in these recent analyses, the $H^+$ associations with respiratory hospital admissions were found to be stronger than for sulfates, or any other PM component monitored. The facts that: (1) these were studies designed specifically to test the hypothesis that $H^+$ is associated with increased respiratory hospital admissions; (2) consistent results were found, both qualitatively and quantitatively across these studies, and; (3) in one of them, many other pollutants and PM metrics were directly intercompared with $H^+$ in the analyses, collectively indicate that these studies provide evidence that acidic aerosols may represent a component of PM which is particularly associated with increases in the incidence of exacerbations in pre-existing respiratory disease.

## TABLE 12-24. COMPARISON OF REGRESSIONS OF DAILY SUMMERTIME RESPIRATORY ADMISSIONS ON POLLUTION AND TEMPERATURE IN TORONTO, ONTARIO, AND BUFFALO, NEW YORK 1988 SUMMER

| City and year | Respiratory admissions category | Temp, pollutant model specification | Pollutant Regression Coefficient (adm/$\mu g/m^3/10^6$, persons ±SE) | Pollutant mean effect (% ±SE) | Max/mean pollutant rel risk (±SE) |
|---|---|---|---|---|---|
| Toronto, 1988 summer | Total respiratory (mean = 14.1/day) | T(LG2), $SO_4^=$(LG1) | 0.07 ± 0.03[a] | 13.3 ± 5.3 | 1.41 ± 0.16 |
| | | T(LG2), $H^+$(LG1) | 0.18 ± 0.009[b] | 7.7 ± 3.9 | 1.50 ± 0.25 |
| | | T(LG2), $O_3$(LG1) | 0.011 ± 0.005[b] | 26.4 ± 11.8 | 1.34 ± 0.15 |
| Toronto, 1988 summer | Total asthma (mean = 9.5/day) | T(LG2), $SO_4^=$(LG1) | 0.04 ± 0.02[b] | 13.0 ± 6.8 | 1.40 ± 0.21 |
| | | T(LG2), $H^+$(LG0) | 0.13 ± 0.07[b] | 8.1 ± 4.5 | 1.53 ± 0.29 |
| | | T(LG2), $O_3$(LG1) | 0.007 ± 0.004[b] | 25.3 ± 14.9 | 1.32 ± 0.19 |
| Buffalo, 1988 summer | Total respiratory (mean = 25.0/day) | T(LG2), $SO_4^=$(LG0) | 0.11 ± 0.04[a] | 8.0 ± 2.7 | 1.25 ± 0.09 |
| | | T(LG2), $H^+$(LG0) | 0.35 ± 0.12[a] | 6.4 ± 2.2 | 1.47 ± 0.16 |
| | | T(LG2), $O_3$(LG2) | 0.015 ± 0.008[b] | 18.4 ± 9.9 | 1.22 ± 0.12 |
| Buffalo, 1988 summer | Total asthma (mean = 7.1/day) | T(LG2), $SO_4^=$(LG1) | 0.03 ± 0.02[b] | 7.0 ± 3.9 | 1.25 ± 0.14 |
| | | T(LG2), $H^+$(LG1) | 0.09 ± 0.05[b] | 5.6 ± 3.3 | 1.43 ± 0.26 |
| | | T(LG2), $O_3$O(LG3) | 0.006 ± 0.002[a] | 23.9 ± 10.1 | 1.29 ± 0.12 |

[a]P<0.01 (one-way test).
[b]P<0.05 (one-way test).

Sources: Thurston et al. (1994b) and Thurston et al. (1992).

### 12.5.3.7 Acute Acid Aerosol Exposure Associations with Mortality

As discussed in the methodological discussions at the outset of this chapter, relatively long records of daily mortality and pollution are required to have sufficient power to discern mortality-pollution associations. Due to the dearth of sufficiently long records of $H^+$ measurements (other than the historical London measurements discussed previously), only a few studies have attempted to evaluate the acute mortality effects of acidic aerosols.

Dockery et al. (1992) investigated the relationship between multiple air pollutants and total daily mortality during the one year period between September 1985 and August 1986 in two communities: St. Louis, MO; and Kingston/Harriman, TN and surrounding counties. In the latter locale, the major population center considered is Knoxville, TN, some 50 Km from the air pollution monitoring site employed. In each study area, total daily mortality was related to $PM_{10}$, $PM_{2.5}$, $SO_2$, $NO_2$, $O_3$, $SO_4^=$, $H^+$, temperature, dew point, and season using autoregressive Poisson models. In St. Louis, after controlling for weather and season, statistically significant associations were found with both prior day's $PM_{10}$ and $PM_{2.5}$, but not with any lags of the other pollutants considered. In the Kingston/Harriman vicinity, $PM_{10}$ and $PM_{2.5}$ approached significance in the mortality regression, while the other pollutants did not. In both cities, very similar $PM_{10}$ coefficients are reported, implying a 16 to 17 percent increase in total mortality per 100 $\mu g/m^3$ of $PM_{10}$. While autocorrelation was accounted for, seasonality was addressed by season indicator (dummy) variables, which may not remove within-season long wave influences. However, the chief areas of concern regarding this study relate to the exposure data. In both places, only one daily monitoring station was employed to represent community exposure levels, and no information regarding the representativeness of these sites are provided (e.g., correlations with other sites' data). More importantly in the case of $H^+$ analyses, the number of days for which pollution data are available for time-series analyses is limited in this data set (e.g., only 220 days had $H^+$ values at the St. Louis site). As discussed in the methodological section, it is expected that roughly at least twice this number of study days are needed to be able to reliably detect PM associations with mortality. Thus, in the words of the authors: "Because of the short monitoring period for daily particulate air pollution, the power of this study to detect associations was limited." A latter data set for six cities (Schwartz et al., 1996) that was also not significant for $H^+$ was discussed in detail earlier in Section 12-3.

Thus, this attempt to correlate human mortality with present day ambient acid aerosol concentrations was unable to find a significant association, but it is not clear to what extent this result was due to the severe lack of power in the analysis (because of the many fewer $H^+$ observations than available for other pollutants). Clearly, there is a critical need for present day replications of the London mortality-acid aerosol studies to be conducted, in order to determine whether these London associations (dominated by wintertime $H^+$, occurring in reduction-type atmospheres) are pertinent to the U.S., where acid aerosol peaks occur primarily in the summertime, in oxidation-type atmospheres.

## 12.5.4 Studies Relating Health Effects to Long-Term Exposure

A limited but growing amount of epidemiologic study data currently exist by which to evaluate possible relationships between chronic exposures to ambient acid aerosols and human health effects. These include one study from Japan relating effects to estimated or measured acidity, and many other North American studies which relate effects to sulfate levels or other surrogate measures thought to roughly parallel acid aerosol concentrations. Moreover, newer epidemiologic studies, which consider measured acid aerosols, now provide more direct insight into the potential chronic effects of particulate strongly acidic aerosols.

### 12.5.4.1 Acid Mists Exposure in Japan

Kitagawa (1984) examined the cause of the Yokkaichi asthma events (1960 to 1969) by examining the potential for exposure to concentrated sulfuric acid mists and the location and type of health effects noted. He concluded that the observed respiratory diseases were due not to sulfur dioxide, but to concentrated sulfuric acid mists emitted from stacks of calciners of a titanium oxide manufacturing plant located windward of the residential area. This was based on the fact that the $SO_3/SO_2$ ratio of 0.48 was much higher than the normal range of 0.02 to 0.05. The higher ratio indicates a higher acid aerosol level. The acid particles were fairly large (0.7 to 3.3 μm) compared with acid aerosols usually seen in the United States of America (see Chapter 3), but were still were in the respirable range. Between 1960 and 1969, more than six hundred patients with respiratory disease were found to have chronic bronchitis, allergic asthmatic bronchitis, pulmonary emphysema and sore throat. In 1969, measures of acid aerosol exposures

were obtained from litmus paper measurements collected near the industrial plant which showed that acid mist particles were distributed leeward of the industrial plant. The author notes that the physiological effects of concentrated sulfuric acid mists (per estimated mass concentration) may be quite different from that of dilute sulfuric acid mists formed by atmospheric oxidation of sulfur dioxide, and that the distinction between the two types of acid mists is very important. It should be noted that morbidity fell markedly after the installation of electrostatic precipitators which reduced $H_2SO_4$ and other particulate matter emissions.

#### 12.5.4.2 Studies Relating Chronic Health Effects to Sulfate Exposures

Franklin et al. (1985) and Stern et al. (1989) reported on a cross-sectional study investigating the respiratory health of children in two Canadian communities that was conducted in 1983 to 1984, in Tillsonburg, Ontario and Portage la Prairie, Manitoba. There were no significant local sources of industrial emissions in either community. In the first town, 735 children aged 7 to 12 were studied and 895 in the second one. Respiratory health was assessed by the measurement of the forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_{1.0}$) of each child, and by evaluation of respiratory symptoms and illnesses using a questionnaire self-administered by the parents. While $NO_2$ and inhalable particles ($PM_{10}$) differed little between these communities, $SO_2$, $SO_4$, and $NO_3$ were higher in Tillsonburg. Historical data in the vicinity of Tillsonburg indicate that average levels of sulfates, total nitrates and ozone ($O_3$) did not vary markedly in the 9-year period proceeding the study. The results show that Tillsonburg children had statistically significantly ($p < 0.001$) lower levels of FVC and $FEV_{1.0}$ than the children in Portage la Prairie (2% and 1.7% lower, respectively). These differences could not be explained by parental smoking or education, cooking or heating fuels, pollution levels on the day of testing or differences in age, sex, height or weight. The differences persisted when children with either cough with phlegm, asthma, wheeze, inhalant allergies or hospitalization before age 2 for a chest illness were excluded from analysis. With the exception of inhalant allergies, which occurred more frequently in Tillsonburg children, the prevalence of chronic respiratory symptoms and illnesses was similar in the two towns. Thus, sulfates were among the pollutants which were higher in the community experiencing reduced lung function and increased inhalant allergies, while $PM_{10}$ mass concentrations were not different between cities.

Ware et al. (1986) have reported results of analyses from the ongoing Harvard study of outdoor air pollution and respiratory health status of children in six eastern and midwestern U.S. cities. Between 1974 and 1977, approximately 10,100 white preadolescent children were enrolled in the study during three successive annual visits to the cities. On the first visit, each child underwent a spirometric examination, and a parent completed a standardized questionnaire regarding the child's health status and other important background information. Most of the children (8,380) were seen for a second evaluation one year later. Data on TSP, $SO_4$, and $SO_2$ concentrations at study-affiliated outdoor stations were combined with data from other public and private monitoring sites to create a record of pollutant levels in each of nine air pollution regions during a one-year period preceding each evaluation, and for TSP during each child's lifetime up to the time of evaluation. Annual mean TSP levels ranged from 32 to 163 $\mu g/m^3$. Sulfur dioxide levels ranged from 2.9 to 184 $\mu g/m^3$, and sulfate levels ranged from 4.5 to 19.3 $\mu g/m^3$.

Analyzing these data across all six cities, Ware et al. (1986) found that frequency of chronic cough was significantly associated ($p < 0.01$) with the average of 24-h mean concentrations of TSP, $SO_2$, and $SO_4$ air pollutants during the year preceding the health examinations. Furthermore, rates of bronchitis and a composite measure of lower respiratory illness were significantly ($p < 0.05$) associated with annual average particle concentrations. However, within the individual cities, temporal and spatial variation in air pollutant levels and symptom or illness rates were not found to be significantly associated. The history of early childhood respiratory illness for lifetime residents was significantly associated with average TSP levels during the first two postnatal years within cities, but not between cities. Also, pulmonary function parameters (FVC and $FEV_{1.0}$) were not associated with pollutant concentrations during the year immediately preceding the spirometry test or, for lifetime residents, with lifetime average concentrations. Ferris et al. (1986), however, reported a small effect on lower airway function (MMEF) related to fine particle concentrations. Spengler et al. (1986) report the occurrence of acid aerosol peak concentrations of 30 to 40 $\mu g/m^3$ (1 h average) in two of the cities during recent monitoring. Overall, these results appear to suggest that risk may be increased for bronchitis and some other respiratory disorders in preadolescent children at moderately elevated levels of TSP, $SO_4$, and $SO_2$ concentrations, which do not appear to be consistently associated with pulmonary function

decrements. However, the lack of consistent significant associations between morbidity endpoints and air pollution variables within individual cities argues for caution in interpreting these results.

Dockery et al. (1989) presented further results from the cross-sectional assessment of the association of air pollution with chronic respiratory health of children participating in the Six Cities Study of Air Pollution and Health. Air pollution measurements collected at quality-controlled monitoring stations included total suspended particulate matter (TSP), particulate matter less than 15 µm ($PM_{15}$) and 2.5 µm ($PM_{2.5}$) aerodynamic diameter, fine fraction aerosol sulfate ($SO_4^=$), $SO_2$, $O_3$, and $NO_2$. This analysis was restricted to the 5,422 10 to 12 years old white children examined in the 1980 to 1981 school year. Five respiratory illness and symptom responses obtained by questionnaire were considered: bronchitis, cough, chest illness, wheeze, and asthma. Each symptom was analyzed using a logistic regression model including sex, age, indicators of parental education, maternal smoking, gas stove, and city. Reported rates of bronchitis, chronic cough, and chest illness during the 1980 to 1981 school year were positively associated with all measures of particulate pollution (TSP, $PM_{15}$, $PM_{2.5}$, and $SO_4$) and positively, but less strongly, associated with concentrations of two of the gases ($SO_2$ and $NO_2$). For children experiencing wheeze, the estimated relative odds (and 95% CI) for $SO_4^=$ between the most and least polluted cities were: 3.1 (0.6 to 16.8) for bronchitis; 2.4 (0.1 to 60.6) for chronic cough, and; 2.9 (0.5 to 15.6) for chest illness. Frequency of earache also tended to be associated with particulate concentrations, but no significant associations were found with asthma, persistent wheeze, hay fever, or non-respiratory illness. No associations were found between pollutant concentrations and any of the pulmonary function measures considered (FVC, $FEV_{1.0}$, FEV0.75, and MMEF). Children with a history of wheeze or asthma had a much higher prevalence of respiratory symptoms, and there was some evidence that the association between air pollutant concentrations and symptom rates was stronger among children with these markers for hyperreactive airways. Results suggest that children with hyperreactive airways may be particularly susceptible to other respiratory symptoms when exposed to these pollutants. The lack of statistical association between pollutant concentrations and measures of both pulmonary flow and volume suggests, however, that these increased rates of illness are not associated with permanent loss of pulmonary function, at least during the preadolescent years. Overall, these data provide further evidence that rates of respiratory illnesses and symptoms are elevated among

children living in cities with high particulate pollution, including sulfates. Sulfates are known to be correlated over time and across cities with $H^+$, based on direct $SO_4^=$ and $H^+$ monitoring subsequently conducted in each of these cities as part of this study.

Dodge et al. (1985) reported on a longitudinal study of children exposed to markedly different concentrations of $SO_2$ and moderately different levels of particulate sulfate in Southwestern U.S. towns. In the highest pollution area, the children were exposed to 3 h peak $SO_2$ levels exceeding 2,500 μg/m$^3$ and annual mean particulate sulfate levels of 10.1 μg/m$^3$. The prevalence of cough (measured by questionnaire) correlated significantly with pollution levels (chi-square for trend = 5.6, p = 0.02). No significant differences existed among the groups of subjects over 3 years, and pulmonary function and lung growth over the study were roughly equal over all groups. The results tend to suggest that intermittent high level exposure to $SO_2$, in the presence of moderate particulate sulfate levels, produced evidence of bronchial irritation (increased cough), but no chronic effect on lung function or lung function growth. These results are consistent with a bronchitis - $H^+$ relationship, to the extent that $SO_2$ or sulfates are indicative of acidic aerosols in these locales.

Chapman et al. (1985) report the results of a survey done in early 1976 that measured the prevalence of persistent cough and phlegm among 5,623 young adults in four Utah communities. The communities were stratified to represent a gradient of sulfur oxides exposure. Community specific annual mean $SO_2$ levels had been 11, 18, 36, and 115 μg/m$^3$ during the five years prior to the survey. The corresponding annual mean sulfate levels were 5, 7, 8, and 14 μg/m$^3$. No gradients for TSP or suspended nitrates were observed. The analyses were made using multiple logistic regression, in order to adjust for confounding factors such as smoking, age and education. Persistent cough and phlegm rates in fathers were about 8 percent in the high $SO_2/SO_4$ exposure community, versus about 3 percent in the other communities. For mothers, the rates in the high $SO_2/SO_4$ exposure community were about 4 percent, as opposed to about 2 percent in the other communities. Both differences were statistically significant, suggesting that communities with higher $SO_2$ and $SO_4$ pollution experience chronically higher respiratory symptom rates in adults.

Stern et al. (1994) reported on a Canadian survey assessing the effects to transported acidic pollution on the respiratory health of children, regional differences in respiratory symptoms and lung function parameters. A cohort of about 4,000 Canadian school children, aged 7 to 11 years,

residing in five rural communities in southwestern Ontario (high exposure area) and in five rural communities in central Saskatchewan (low exposure area) were examined. Respiratory health status was assessed through the use of parent-completed questionnaires and standard pulmonary function tests performed by the children in the schools. The levels of particulate sulfates and nitrates varied little among communities within each region, but sulfate means did differ between regions, with annual average sulfate readings for 1980 of 1.9 $\mu g/m^3$ and 6.6 $\mu g/m^3$ in Saskatchewan and Ontario, respectively. There were no significant differences in $PM_{10}$ between these regions, however. After adjusting for the effects of age, sex, parental smoking, parental education and gas cooking, no differences in the prevalence of chronic cough, chronic phlegm, persistent wheeze, current asthma, bronchitis in the past year, or any chest illness that kept a child home for 3 or more days in the previous year most days and nights were observed. This differs with the results of the Harvard Six City Study (Dockery et al., 1989), which Stern et al. (1994) conclude may be due to a threshold of effects for chronic air pollution and respiratory symptoms effects. There were no regional differences in PEFR, $FEF_{25-75}$, $FEF_{75-85}$, $Vmax_{5O}$, and $Vmax_{25}$. However, statistically significant decrements of 1.7% in FVC and 1.3% in $FEV_{1.0}$ were observed in Ontario children, as compared with those in Saskatchewan, after adjusting for age, sex, weight, standing height, parental smoking, and gas cooking. These results are noted to be similar to those reported by Schwartz (1989), but not with the Six-Cites results (Dockery et al., 1989). It is hypothesized that this new study had greater power to detect such effects because the areas being contrasted are more similar, other than with respect to air pollution. The authors conclude that statistically significant decrement in the pulmonary volume parameters, FVC and $FEV_{1.0}$, of preadolescent children residing in rural southwestern Ontario are associated with moderately elevated ambient concentrations of sulfates and ozone.

Schenker et al. (1983b) studied 5,557 adult women in a rural area of western Pennsylvania using respiratory disease questionnaires. Air pollution data (including $SO_2$, but not particulate matter measurements) were derived from 17 air monitoring sites and stratified in an effort to define low, medium and high pollution areas. The four-year means (1975 to 1978) of $SO_2$ in each stratum were 62, 66, and 99 $\mu g/m^3$, respectively. Respiratory symptom rates were modeled using multiple logistic regression, which controlled for several potentially confounding factors, including smoking. A model was used to estimate air pollutant concentrations at population-weighted

centroids of 36 study districts. The relative risk (odds ratio) of "wheeze most days or nights" in nonsmokers residing in the high and medium pollution areas was 1.58 and 1.26 (p 0.02) respectively, as compared with the low pollution area. For residents living in the same location for at least five years, these relative risks were 1.95 and 1.40 ($p < 0.01$). Also, the increased risk of grade 3 dyspnea in nonsmokers was associated with $SO_2$ levels (p 0.11). However, no significant association was observed between cough or phlegm and air pollution variables. The results of this study may indicate that wheezing can be associated with $SO_2$ levels, but these results must be viewed with caution, since the gradient between areas was small and there were no particle or other pollutant measures. Lippmann (1985) suggested that it was plausible that the effects in this study are associated with submicrometer acid aerosol, which deposits primarily in small airways, rather than with $SO_2$ levels.

Jedrychowski and Krzyzanowski (1989) related $SO_2$ and PM levels to increased rates of chronic phlegm, cough and wheezing in females living in and near Cracow, Poland. The authors conjecture that the effects may have been due to hydrogen ions, but no direct measurements were available.

Several authors (Lave and Seskin, 1972, 1977; Chappie and Lave, 1982; Mendelsohn and Orcutt, 1979; Lipfert, 1984; Ozkaynak and Spengler, 1985; Ozkaynak and Thurston, 1987) have related annual mortality rates in U.S. Metropolitan Statistical Areas (MSA's) to sulfate and other pollution measurements using aggregate population cross-sectional analyses. There are significant problems and inconsistencies in results obtained across many of these analyses, as reviewed extensively by the U.S. Environmental Protection Agency (1986a, 1982). For example, Lave and Seskin (1977) reported that mortality rates were correlated with sulfates. Lipfert (1984), reanalyzing the same data using new variables, found that it was not possible to conclude whether sulfates or particulate matter had a statistically significant effect on total mortality in that it was difficult to separate the effects of sulfates from TSP on total mortality, even when sulfate is subtracted from TSP. These studies are reviewed in more detail in Section 12.4.1, but are included again in this section because of their relevance to acid aerosol epidemiology.

Ozkaynak and Spengler (1985), Ozkaynak et al. (1986), and Ozkaynak and Thurston (1987) employed a variety of model specifications and controls for possible confounding, and used more sophisticated statistical approaches in an effort to improve upon some of the previous analyses of

mortality and morbidity associations with air pollution in U.S. cities. The principal findings concern cross-sectional analysis of the 1980 U.S. vital statistics and available air pollution data bases for sulfates, and fine, inhalable and total suspended particles. In these analyses, using multiple regression methods, the association between various particle measures and 1980 total mortality were estimated for 98 and 38 SMSA subsets by incorporating information on particle size relationships and on a set of socioeconomic variables to control for potential confounding. Model misspecification and spatial autocorrelation of the residuals issues were also investigated. Results from the various regression analyses indicated the importance of considering particle size, composition, and source information in modeling of PM-related health effects. In particular, particle exposure measures related to the respirable and/or toxic fraction of the aerosols, such as FP (fine particles) and sulfates were the most consistently and significantly associated with the reported (annual) cross-sectional mortality rates. On the other hand, particle mass measures that included coarse particles (e.g., TSP and IP) were often found to be nonsignificant predictors of total mortality. Part of the relative insensitivity of coarse particles could have resulted from greater spatial variability across an SMSA and the use of a single monitoring station (see Chapter 7). In addition, an analysis of source-related fine particle trace element components for the 38 SMSA set found the strongest mortality associations with industrial and combustion-related components of the fine aerosol, but not with soil-derived particles. Thus, these analyses suggest that sulfate and associated fine combustion-related particles were most closely associated with mortality.

The Ozkaynak and Thurston (1987) results noted above for analysis of 1980 U.S. mortality provide an interesting overall contrast to the findings of Lipfert (1984) for 1969 to 1970 U.S. mortality data, and to the findings of Lipfert et al. (1988) for the 1980 U.S. mortality data. In particular, whereas Lipfert found TSP coefficients to be most consistently statistically significant (although varying widely depending upon model specifications, explanatory variables included, etc.), Ozkaynak and Thurston (1987) found particle mass measures, including coarse particles (TSP, IP), often to be nonsignificant predictors of total mortality. Also, whereas Lipfert found the sulfate coefficients to be even more unstable than the TSP associations with mortality (and questioned the credibility of the sulfate coefficients), Ozkaynak and Thurston (1987) found that particle exposure measures related to the respirable or toxic fraction of the aerosols (e.g., FP or

sulfates) to be most consistently and significantly associated with annual cross-sectional mortality rates. They estimated a range of particulate matter-total mortality mean effects of 4 to 9% of total U.S. mortality, when sulfates were used as the PM metric. When Lipfert (1988) conducted a reanalysis of the 1980 cross-sectional dataset, and added many more controllers for confounding (e.g., for smoking, water hardness and sulfate artifact), he also reports a significant sulfate coefficient having an elasticity of 2.8 to 13%, which is not statistically different from that reported by Ozkaynak and Thurston (see Lipfert and Morris, 1991, and; Thurston and Ozkaynak, 1992 for discussion). Thus, while results vary somewhat across studies, most cross-sectional analyses of the 1960, 1970, and 1980 data found an association between some measure of chronic PM exposure and increased human mortality. The degree to which sulfate is identified depends on the model specification used in the analysis.

Taken as a whole, these various analyses are usually, but not always, indicative of mortality and morbidity associations with the sulfate fraction of fine particles found in contemporary American urban airsheds. Variations in the acidity of the sulfate fraction may explain this apparent variability in sulfate toxicity. However, without nationwide measurements of airborne acidity, it is difficult to evaluate the relative contribution of acid aerosols within these fine particle sulfates to the reported health effects.

### 12.5.4.3 Studies Relating Chronic Health Effects to Acid Aerosols

In an hypothesis generating discussion, Speizer (1989) presented city-specific bronchitis prevalence rates from the six cities. While no direct aerosol acidity measurements were made during or before the 1980/81 school year (when the children were examined), Speizer (1989) used pollution data that Spengler et al. (1989) gathered in Kingston/Harriman and St. Louis from December 1985 through September 1986 and in Steubenville and Portage from November 1986 to early September 1987. His plot of bronchitis prevalence as a function of $PM_{15}$ is presented in Figure 12-15. Additional $H^+$ concentration data from Watertown, MA and Topeka, KS have since been published by Dockery (1993), and all these data are included in the updated version of Speizer's $H^+$ plot presented in Figure 12-16. It should be noted that these points may contain unaddressed bronchitis variation due to factors other than pollution. For example, illness and hospitalization rates are known to vary across areas, independent of health status factors (Wennberg, 1987; McPherson et al., 1982). Thus, the relationship of bronchitis rates with pollution in these preliminary analyses must be considered as being only suggestive. However, as seen in these figures, when the city-specific bronchitis rates are plotted against mean $H^+$ concentrations, instead of $PM_{15}$, there is a relative shift in the ordering of the cities which suggests a better correlation of bronchitis prevalence with $H^+$ than with $PM_{15}$.

Damokosh et al. (1993) and later Dockery et al. (1996) report analyses of the 6-City children's bronchitis data more thoroughly by incorporating controls for confounding variables, and by addin a seventh locale, Kanahwa County, WV to the analysis. In that county, $PM_{10}$, $PM_{2.5}$, and $H^+$ were measured from 1987 to 1988 during the collection of data on the respiratory health status of 7,910 children in third through fifth grade. As in the 6-City study, respiratory health status was assessed in Kanahwa County via a parent completed questionnaire. Nine indicators of asthmatic and bronchitic symptom reports were considered. A two-stage logistic regression analysis was used, adjusting for maternal

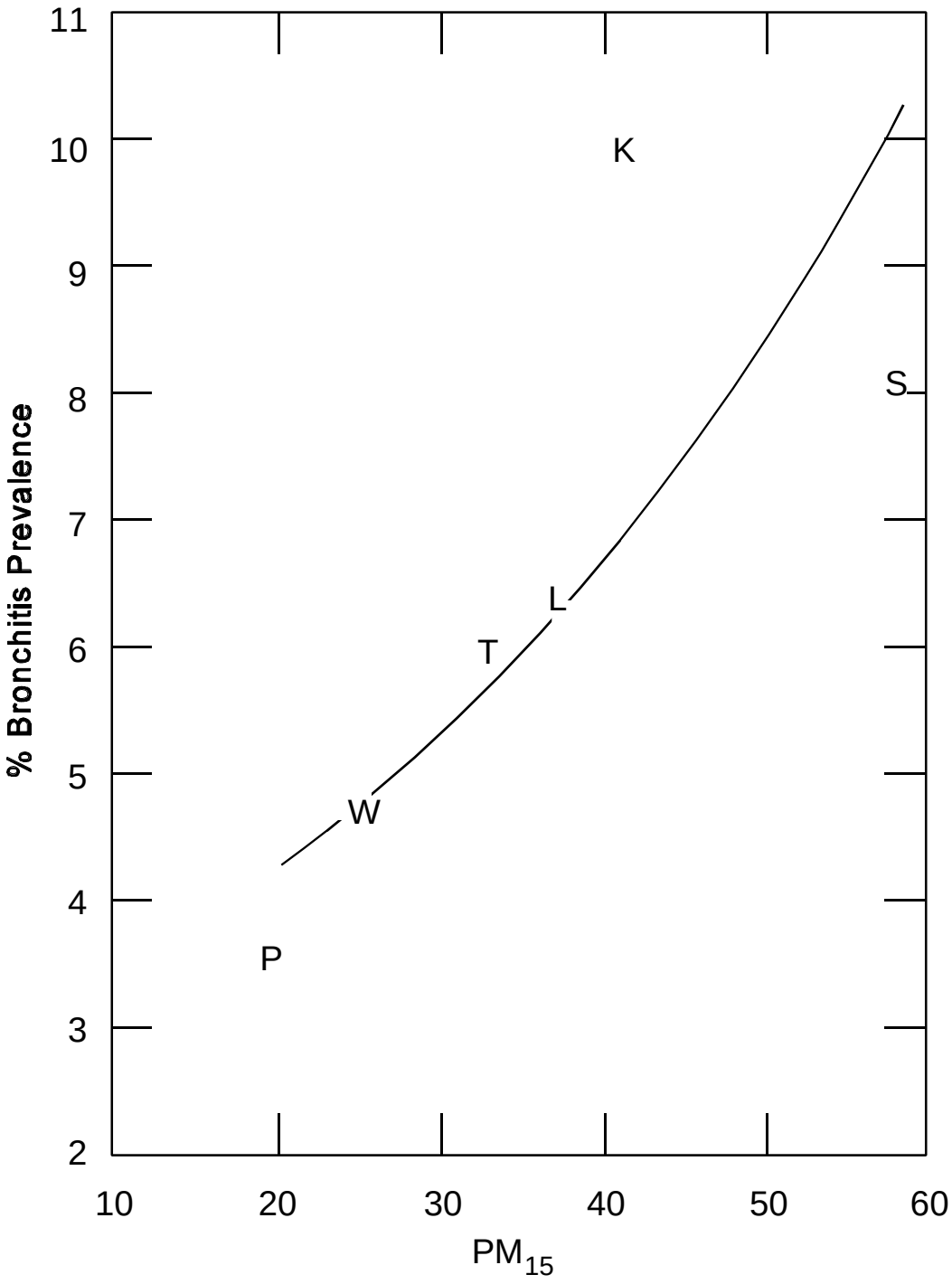


**Figure 12-15. Bronchitis in the last year, children 10 to 12 years of age in Six Cities, by $PM_{15}$ (P = Portage, WI; T = Topeka, KS; W = Watertown, MA; K = Kingston, TN; L = St. Louis, MO; S = Steubenville, OH.)**

Source: Speizer (1989).

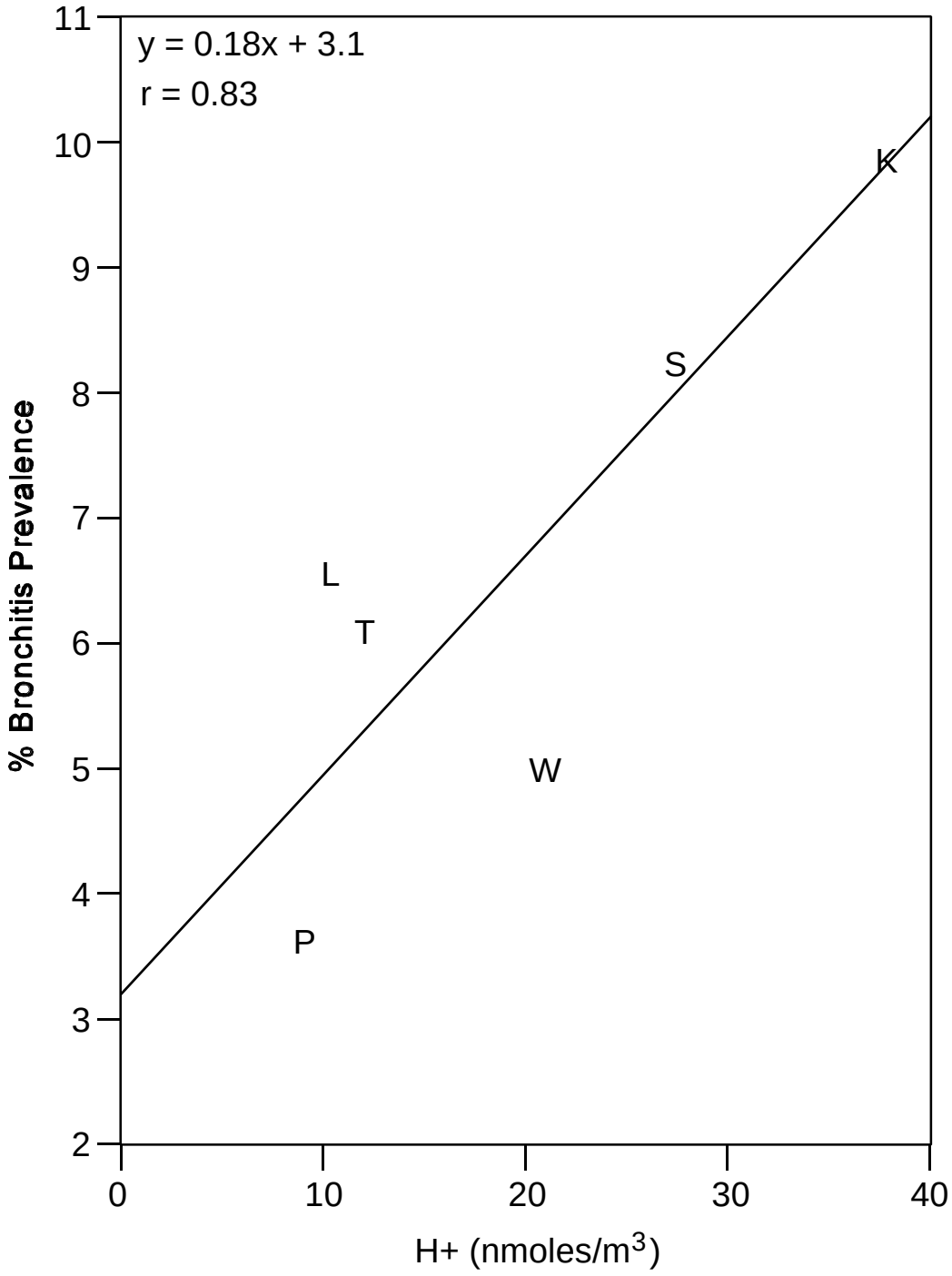


**Figure 12-16. Bronchitis in the last year, children 10 to 12 years of age in six U.S. cities, by hydrogen ion concentration. (K = Kingston, TN; L = St. Louis, P = Portage, WI; S = Steubenville, OH; T = Topeka, KS; W = Watertown, MA.)**

Source: Dockery (1993); Speizer (1989).

smoking and education, race, and any unexplained variation in symptom rates between the cities. Significant associations were found between summer mean $H^+$ and chronic bronchitis and related symptoms (cough, phlegm, and chest illness). The estimated relative odds for bronchitic symptoms associated with the lowest mean value of particle strong acidity (15.7 nmoles/$m^3$) to the highest (57.8 nmoles/$m^3$) was 2.4 (95% CI: 1.9 to 3.2). No associations were found for asthma or asthma related symptoms (doctor diagnosed asthma, chronic wheeze, and wheeze with attacks of shortness of breath). However, equivalent results were found with other particle mass measurements highly correlated with aerosol acidity.

As a follow-up to the 6-City study, the relationship of respiratory symptom/illness reporting with chronic exposures to acidic aerosols was tested among a cohort of schoolchildren in 24 rural and suburban communities in the United States and Canada (Dockery et al., 1996). Ambient air pollution concentrations were measured for one year in each community. Annual mean particulate strong acidity concentrations ranged from 0.5 to 52 nmoles/$m^3$ across the 24 communities. Questionnaires were completed by the parents of 15,523 schoolchildren 8 to 12 years of age. Both bronchitic symptoms, (reports of bronchitis, cough, or phlegm) and asthmatic symptoms, (reports of asthma, shortness of breath with wheeze) or persistent wheeze, were considered separately. City-specific reporting rates were first calculated after adjustment for the effects of gender, age, parental asthma, parental education, and parental allergies. Associations with ambient air pollution were then evaluated. Bronchitic symptoms were associated with particulate strong acidity: relative odds 1.66 (95% CI: 1.11 to 2.48) across the range of exposures. Increased reporting of bronchial symptoms were also associated with other measures of particulate air pollution including sulfate - relative odds 1.65 (95% CI: 1.12 to 2.42). However, associations of asthmatic symptom reports with any of the air pollutants, including particulate acidity, were not statistically significant. Stratified analyses did not show any evidence that asthmatics or other potentially sensitive groups of children had a greater response to particulate acidity.

Raizenne et al. (1996) drew upon the same cohort of children described above to specifically examine the health effects in children of living in regions having periods of elevated ambient acidic air pollution (22 communities in the U.S. and Canada, 8 sites/year, 3 years) . Parents of children 8 to 12 years old completed a questionnaire and provided consent for their child to perform a

standardized forced expiratory maneuver on one occasion between October and May. Air and meteorological monitoring were performed in each community for the year preceding the pulmonary function tests. The annual mean particle strong acidity ($H^+$) ranged from 0.5 to 52 nmoles/$m^3$, $PM_{10}$ from 18 to 35 µg/$m^3$, and $PM_{2.1}$ from 6 to 21 µg/$m^3$. Annual $H^+$ was more highly correlated with $PM_{2.1}$ (r = .72) and $SO_4$ (r = .91) than with $PM_{10}$ (r = 0.29). FVC and $FEV_1$ measurements of 10,251 Caucasian children in 22 communities were used in a two-stage logistic regression analysis, adjusted for age, sex, height, weight, sex-height interaction and parental history of asthma. The reported effect estimates were expressed in terms of 52 nmoles/$m^3$ difference in $H^+$. The results indicated that residing in high particle strong acidity regions was associated, on average, with a 3.45% (95% CI 4.87, 2.01) and a 3.11% (95% CI 4.62, 1.58) lower than predicted FVC and $FEV_{1.0}$, respectively. For children with a measured FVC less than or equal to 85% of predicted, the odds ratio for lower lung function was 2.5 (95% CI 1.8, 3.6) across the range of $H^+$ exposures. Assuming that these exposures reflect lifetime exposure of the children in this study, the data suggest that long-term exposure to ambient particle acidity may have a deleterious effect on normal lung growth, development, and function.

As discussed in detail earlier in this chapter, Dockery et al. (1993) reported results of a prospective cohort study that examined the effects of air pollution on mortality, controlling for individual risk factors. Survival analysis, including Cox proportional-hazards regression modeling, was conducted with data from a 14 to 16 year mortality follow-up of 8,111 adults in six U.S. cities. After adjusting for smoking and other risk factors, statistically significant associations were found between air pollution and mortality. Using inhalable particles, fine particles, or sulfates as the indicator of pollution all gave similar results: an adjusted mortality-rate ratio for the most polluted city as compared to the least polluted city of 1.26 (95% CI = 1.08 to 1.47). Weaker mortality associations were found with $H^+$ in this analysis. However, the $H^+$ data employed may not be appropriate for such an analysis. Of the pollutant data considered, the $H^+$ was the most limited; less than one year of $H^+$ data collected in each city near the end of the study were used to characterize lifetime exposures of adult study participants. This seems especially inappropriate in Steubenville, OH where the industrial (e.g., steel mill) pollution levels diminished during the course of the study, as the steel industry in the valley declined. Indeed, in Steubenville, the $H^+$ data were only collected from mid-October, 1986 through early September, 1987

(Spengler et al., 1989). In contrast, the inhalable particle, fine particle, and sulfate data used for each city were more representative, having been collected earlier and over a five to six year period. Thus, not finding a statistically significant correlation between $H^+$ and mortality (relative to sulfates and fine particles) may be due in large part to the fact that the limited $H^+$ data employed were not sufficient for this application.

#### 12.5.4.4 Chronic Exposure Effects in Occupational Studies

The last remaining type of information considered here concerns the effects of chronic exposures to acid aerosols in occupational settings. Such studies are discussed mainly in order to provide some perspective on the variety of health effects associated with acid aerosol exposures, albeit at extremely high concentrations not likely to occur in ambient air.

Gamble et al. (1984a) studied pulmonary function and respiratory symptoms in 225 workers in five lead battery acid plants. This acute effect study obtained personal samples of $H_2SO_4$ taken over the shift. Most personal samples were less than 1 mg/m$^3$ $H_2SO_4$, and mass median aerodynamic diameter of $H_2SO_4$ averaged about 5 μm. The authors concluded that exposure to sulfuric acid mist at these plants showed no significant association with symptoms or acute effects on pulmonary function. The ability of the body to neutralize acidity of $H_2SO_4$ was considered as one factor in this outcome. Also, the authors speculated that tolerance to $H_2SO_4$ may develop in habitually exposed workers.

In a related study of chronic effects of sulfuric acid on the respiratory system and teeth, Gamble et al. (1984b) measured in the same workers respiratory symptoms, pulmonary function, chest radiographs, and tooth erosion. Concentrations of $H_2SO_4$ at the time of the study were usually 1 mg/m$^3$ or less. Exposures to such acid mist levels showed no significant association with cough, phlegm, dyspnea, wheezing, most measures of pulmonary function, and abnormal chest radiographs. Tooth etching and erosion were strongly related to acid exposure. The authors noted that the absence of a marked effect of acid exposure on respiratory symptoms and pulmonary function may be due to the size of the acid particles, ranging in the 5 plants from 2.6 to 10 μm, MMAD which is much larger than typically <1.0 $\mu$m) ambient $H^+$ aerosols. Moreover, the relative humidity of the lung may cause at least a doubling of particle size, especially in the lower size range. Thus, most acid particles may be deposited in the upper respiratory tract and

many may not even reach the lung. Finally, the authors note that the lack of any convincing finding in this study related to acute respiratory symptoms is not completely unexpected, due to the relatively low exposure (<1 $mg/m^3$) compared to previous occupational studies.

Williams (1970) studied sickness absence and ventilatory capacity of workers exposed to high concentrations of sulfuric acid mist in the forming department of a battery factory (location not stated). Based on 38 observations made on two days, the forming department had a mean $H_2SO_4$ concentration of 1.4 $mg/m^3$, ranging from a trace to 6.1 $\mu g/m^3$. In a different forming department, the mass median diameter of the acid particles was 14 µm. Compared with control groups, men exposed to the high concentrations of sulfuric acid mist in the forming department had slight increases in respiratory disease, particularly bronchitis. There was no evidence of increased lower respiratory disease, which might be explained by the large particle size. After adjusting for circadian variations, there was no evidence of decreased ventilatory function.

Beaumont et al. (1987) studied mortality patterns in 1,165 workers exposed to sulfuric acid and other acid mists in steel-pickling operations. Workplace monitoring during the 1970's indicated worker personal exposures to average 190 $\mu g/m^3$ $H_2SO_4$. However, as discussed for battery plant operations, the particle size of these mists tend to be larger than ambient acid aerosols, so not all is likely to be respirable. Standardized mortality ratio (SMR) analysis of the full "any acid exposure" cohort (n = 1,165), with the use of U.S. death rates as a standard, showed that lung cancer was significantly elevated, with a mortality ratio of 1.64 (95%CI = 1.14 to 2.28, based on 35 observed deaths). The lung cancer mortality ratio for workers exposed only to sulfuric acid (n = 722) was lower (SMR = 1.39), but further restriction to the time 20 years and more from first employment in a job with probably daily sulfuric acid exposure (~0.2 $mg/m^3$) yielded a mortality ratio of 1.93 (95% CI = 1.10 to 3.13). An excess lung cancer risk was also seen in workers exposed to acids other than sulfuric acid (SMR = 2.24; 95% CI = 1.02 to 2.46). When comparison was made to other steel workers (rather than to the U.S. general population) to control for socio-economic and life-style factors such as smoking, the largest lung cancer excess was again seen in workers exposed to acids other than sulfuric acid (SMR = 2.00; 95% CI = 1.06 to 3.78). However, the smaller rate ratios may have been partly due to the restriction of this sub-analysis to white males, which excluded the higher excess lung cancer risk in nonwhite males. Adjustment for potential differences in smoking habits showed that increased smoking was

unlikely to have entirely explained the increased risk. Mortality from causes of death other than lung cancer was unremarkable, with the exception of significantly lower rates for deaths due to digestive system diseases. These results suggest that chronic acid aerosol exposures may promote lung cancer at high concentrations, perhaps via chronic irritation of respiratory tissues, or by some other mechanism (e.g., by affecting clearance rates in the lung).

### 12.5.5 Summary of Studies on Acid Aerosols

Historical and present-day evidence suggest that there can be both acute and chronic effects by strongly acidic PM on human health. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations (on the order of 400 $\mu g/m^3$ as $H_2SO_4$, or roughly 8,000 nmoles/$m^3$ $H^+$) may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and $SO_2$. In addition, Thurston et al. (1989) and Ito et al. (1993) both found significant associations between acid aerosols and mortality in London during non-episode pollution levels ( 30 $\mu g/m^3$ as $H_2SO_4$, or approximately 600 nmoles/$m^3$ $H^+$), though these associations could not be separated from those for BS or $SO_2$. The only attempts to date to associate present-day levels of acidic aerosols with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993, Schwartz et al., 1996) failed to do so, but there may not have been a sufficiently long series of $H^+$ data to detect $H^+$ associations. In recently reported Utah Valley, $PM_{10}$ studies (Pope et al. 1991, 1992), $PM_{10}$-health effects association were found, despite limited $H^+$ sampling indicating low acid aerosol levels. This is not inconsistent with adverse health effects from $H^+$, however, when it is considered that PM can contain numerous toxic agents other than $H^+$. There is a critical need for present day replications of the extensive London mortality-acid aerosol studies to be conducted, however, in order to determine if the London wintertime health effects associations (which occurred predominantly in wintertime reduction-type atmospheres) are pertinent to present-day U.S. conditions, in which acid aerosol peaks occur primarily in the summer months (in oxidation-type atmospheres).

Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has now been observed under present-day conditions, as well. Thurston et al. (1992) and Thurston et al. (1994b) have noted associations

between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding temperature effects. In the latter of these studies, significant independent $H^+$ effects remained even after simultaneously considering the other major co-pollutant, $O_3$, in the regression model. While the New York State study considered only ozone as a possible confounder, the Toronto study also considered $NO_2$ and $SO_2$, but found them to be non-significant. In the Toronto analysis, the increase in respiratory hospital admissions associated with $H^+$ was indicated to be roughly six times that for non-acidic $PM_{10}$ (per unit mass). In these studies, $H^+$ effects were estimated to be the largest during acid aerosol episodes ($H^+$ 10 $\mu g/m^3$ as $H_2SO_4$, or 200 nmoles/$m_3$ $H^+$), which occur roughly 2 to 3 times per year in eastern North America. These studies provide evidence that present-day strongly acidic aerosols can represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic PM effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate $H^+$ associations with lower respiratory symptoms except at $H^+$ above 110 moles/$m_3$ (Schwartz et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of $H_2SO_4$ (Schwartz, et al., 1991b). Some, but not all, recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with $O_3$ (Studnicka et al., 1995; Neas et al., 1995).

Studies of the effects of chronic $H^+$ exposures on children's respiratory health and lung function are generally consistent with effects as a result of chronic $H^+$ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average $H^+$ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested associations between summertime average $H^+$ and chronic bronchitic and related symptoms (Damokosh et al., 1993; Dockery et al., 1996). The relative odds of bronchitic symptoms with the highest acid concentration (58

nmoles/$m^3$ $H^+$) versus the lowest concentration (16 nmoles/$m^3$) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1996) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.66, 95% CI: 1.11 to 2.48). It was also found that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1996). Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children.

## 12.6 DISCUSSION

### 12.6.1 Introduction and Basis for Study Evaluation

The epidemiologic studies of human health effects related to PM exposure play a particularly important role because there is somewhat less supporting information on exposure-response information from toxicological or clinical studies compared to other criteria pollutants. We have therefore paid special attention to methodological issues in the studies that have been reviewed in this epidemiology chapter. Various health endpoints have been used in these studies, including respiratory function measures, respiratory symptom reports, hospital admissions, total non-accidental mortality, and mortality classified by medical cause of death such as respiratory or cardiovascular classifications. Each health outcome has many causes other than air pollution, and no specific air pollutant can be uniquely associated with a specific outcome, including PM and its components. Subject-specific (personal) exposure to PM or to other air pollutants is unmeasured in almost all of the studies, and exposure to PM, to other pollutants, or even to weather variables, is only estimated from one or a few monitoring sites in a large metropolitan area or region. Demographic information can be used with either longitudinal studies, prospective studies, or cross-sectional studies, but age is the only individual subject variable that has been used in almost all studies. Other personal variables can be obtained in prospective studies. Comparisons across different cities must be adjusted for demographic and climatologic differences, and usually are in cross-sectional studies. Studies of acute responses to air pollutants, whether measured by

respiratory function indices, respiratory symptoms, hospital admissions, or mortality, have been compared by various formal or informal meta-analytic techniques (Schwartz, 1992a, 1994c; Dockery and Pope, 1994b), but there has so far been no effort to adjust the results of the metaanalyses for quantitative differences among study groups or for differences in data-analytic methodologies.

Many of the differences in results cannot reasonably be attributed to differences in methods of data analysis. Very similar estimates of the effects of PM can be obtained for a wide range of alternative data analysis methods. Ideally, models for short-term effects should be adjusted for seasonality, for long-term and transient irregular events such as influenza epidemics, for auto- and cross-correlation structure when necessary, for sensitivity to distributional assumptions such as Poisson or hyper-Poisson variability and, if not based on demonstrably robust methods, for sensitivity to unusual values among either predictor or response data. Models used in the individual studies in EPA meta analyses, have generally met most of these criteria.

#### 12.6.1.1 Differences Among Study Results

What is more disturbing is that, using similar data sets, different investigators of acute mortality effects have derived different estimates of PM effect size or statistical significance. There are at least two possible reasons for this. The first is that there may be some genuine confounders of PM effects on human health. In some studies, under some meteorological or seasonal conditions, co-pollutants will be emitted by some of the same sources as emit PM, so that there will be a close intrinsic relationship between PM and some other pollutants. This may also extend to certain meteorological variables, which may be related both to atmospheric dispersion of all outdoor pollutants and to pollutant emissions rates. For example, an extremely hot day in summer may be associated with increased use of electrical power for air conditioning (increasing emissions of PM and other pollutants such as $SO_2$ from local electricity generating plants that burn fossil fuels) and, also, with increased motor vehicle use as people travel to less uncomfortable locations (increasing vehicle-generated pollutants from gasoline and other motor vehicle fuels, including $O_3$, CO, and $NO_2$). Primary gaseous pollutants may become secondary atmospheric sources of certain PM components, such as sulfates and nitrates. While there are a number of statistical diagnostics for intrinsic confounding, and even a few adequate methods for

partially resolving seriously confounded predictors of response, these have rarely been used. Analyses in which only a single pollutant is used to predict a health effect are not wholly satisfactory without confirmation by multi-pollutant analyses, adjusted for confounding insofar as possible. In this regard, comparison across different studies, including those in which each potentially confounding factor is or is not present, may be needed to assess the effects of PM in the absence of detailed technical assessments of sensitivity to intrinsically confounded variables.

The second reason why different investigators may derive different results for acute mortality is much more profound. In the absence of generally acceptable mechanistic relationships among potentially confounding variables, and in the absence of generally acceptable specifications for the exposure-response relationships for PM, for co-pollutants, and for weather, all modelling is data-driven and empirical. This has led almost all investigators into extensive model specification searches, in which numerous alternative models may be fitted to the same data or to subsets of the same data set until a "best fitting" or "statistically significant" model is obtained. It has long been known (Leamer, 1978) that data-driven model specification searches can seriously distort the actual significance level of the regression coefficients in ordinary linear regression models with independent Gaussian errors, and by extension we expect the same problem in Poisson and hyper-Poisson exponential regression models with complicated correlation structures. This is similar to the better-known "multiple comparisons" problem, in which all possible subsets of a set of hypothesis tests in a linear analysis of (co)variance could be tested, with a corresponding artificial inflation of the statistical significance of the whole ensemble of tests. However, the complicated model specification searches that have produced the models reported in the published PM epidemiologic studies have a hypothetically limitless number of alternative specifications.

In evaluating model specification options, a model specification search may be extended until some combination of correlation model or lag structure, adjustments for time trends, season, co-pollutants, and weather produces a model in which the study response data are fitted well and the PM coefficient is "statistically significant". Statistical significance for a PM coefficient means that either an asymptotic confidence interval or a more exact likelihood ratio-based confidence interval for the effect does not cover the null value (0 for effect size, 1 for relative risk). Or, the specification search may proceed towards the goal of establishing that some other pollutant in the

model is a statistically significant predictor of changes in mortality rates or hospital admission rates (etc.) or that some combination of meteorological variables can fit the observed health effects data when the PM coefficient is not statistically significant. This could provide the basis of an argument that some factor(s) other than PM are accounting for the observed effects. Because of the confounding that exists between PM and other variables that may be used in the models, there may be many substantial points of similarity between the models with a significant PM effect and those without a significant PM effect, at least in some cities during some years. There may thus be little internal basis for choosing between two models, one with a significant PM effect and another, using similar specifications in many ways, without a significant PM effect.

There are several ways in which the indeterminacy of the models from different studies of the same data set could be resolved. The first method, and in many ways the best, is to see which of the competing models does the best job of predicting new information. Since new information is not readily at hand, a more realistic method would be "internal cross-validation". The model would be fitted to one subset of the data and then the parameters derived from the model based on one part of the data would be used to predict the other part. In time series analysis, the use of the first part of the series to predict the last part of the series is known as "postdiction", to distinguish the exercise from a genuine forecast or prediction in which the future observations and their predictors are in fact unknown. A related approach would be to use the PM and co-pollutant models derived from one group of cities to estimate health effects in another group of cities, where "pre-models" specific to each of the second group of cities are used to adjust mortality rates for all non-pollution variables such as meteorological variables. In practice, we are not aware of any efforts to assess the predictive validity of any of the models, either in an absolute sense or relative to a competing model.

#### 12.6.1.2 Importance of Comparisons Across Different Cities

We are therefore limited to evaluating models reported in different studies on the basis of comparisons of results for different geographic sites (cities, SMSA's, etc.) or during different periods of time. If the estimated PM effect is similar in magnitude across a range of different cities, differing in location, climate, co-pollutant inventories, demographics, or other relevant factors, we may argue that these effect estimates are relatively robust with respect to exact specifications of different models. This is discussed in more detail in Section 12.6.3.

Similarly, weather is an important confounding factor. Adjustments for meteorological variables may differ substantially from one study to another. It is easier to compare effect size estimates from studies with similar adjustment methods. However, there are likely to be real differences among cities that complicate the use of weather effect models found at one location to adjust for weather effects on human health in another location. This is particularly likely to affect adjustments made for extreme weather conditions, whether defined by a threshold for a temperature effect or by a weather-related synoptic category. It is, in any event, easier to identify a quantitative PM relationship during non-extreme weather conditions, or during non-offensive synoptic categories. Studies in which the size of the PM exposure-response relationship was estimated for non-extreme weather conditions, or for which appropriate adjustments were made in the analysis, are also accorded higher weight than those without such distinctions.

Finally, there is a question about how the effect size estimates in different cities should be combined, or whether there should be a combined estimate. Combined estimates using meta-analytic techniques have been published (Schwartz, 1994c; Dockery and Pope, 1994b), and additional meta-analyses for the more recent studies may be useful. However, there is a possibility that real differences exist among PM effect sizes in different communities. The differences may be due to differences in area-specific PM composition, in sub-populations, in pre-existing health status, in acclimatization to weather conditions, or to effects of other unmeasured air pollutants. If the differences among communities are substantial, it may be preferable to treat the PM effect on health outcome as a random effect across communities, even though the reasons for the differences are potentially explainable, but unknown at present.

### 12.6.1.3 Sample Size and Power of Reported PM-Mortality Associations

Since the size of the 'relative risks' and the extent of associations found in recent observational studies of PM-mortality are not 'large', such associations are unlikely to be shown in a 'small' sample size (i.e., a limited number of days). This can be particularly problematic if one plans to analyze the data using PM data collected at the current U.S. sampling frequency (i.e., every-6th-day). It should be noted that a majority of the existing studies that reported significant PM-mortality associations used PM data that were collected daily. A determination of the sample size required to find the observed association in a given community is not simple, because power may be dependent on not only sample size, but also on: (1) the population size of the community (to produce certain number of deaths per day); (2) the levels of PM; (3) the proportion of susceptible populations (e.g., age/race/gender distribution); (4) the location and number of PM sampling sites to estimate representative PM exposure of the population, and; (5) the model specification. Also, determining the expected 'effect' size from the published studies alone may be misleading because of potential 'publication bias' towards significant effects. With this caveat in mind, one can illustrate the effects of sample size and the above mentioned factors on the significance of PM/total daily mortality associations, by examining the t-ratios of the PM coefficients reported by recent U.S. PM-mortality studies (Table 12-25). When both multi-pollutant models and single pollutant models were presented, a single pollutant model was selected here. All the models included weather variables. When both Poisson models (log-linear GLM) and OLS models were presented (Schwartz, 1993a; Kinney et al., 1995), both gave essentially identical t-ratios, and therefore the results for Poisson models are shown. Despite the magnitude of differences in various studies' population/mean deaths, the key predictor of t-ratio appears to be the number of study days (sample size).

In a simple linear regression, the t-ratio for the null hypothesis of a regression coefficient being zero is a function of square-root of sample size, with its slope being $r/(1-r^2)^{0.5}$, where r is the underlying size of the correlation between the dependent variable (e.g., mortality) and the explanatory variable (e.g., PM). The plot (Figure 12-17) of these t-ratios versus square-root of sample days from Table 12-25 in fact shows the t-ratio's strong linear dependency on the square-root of sample size. The magnitude of PM-mortality associations seen in these studies, as reflected in the slope (r=0.083, if the slope is equated to $r/(1-r^2)^{0.5}$, requires about n=600 days for the association to be significant at 0.05 (two-tailed), or n=400 for one-tailed test at 0.05 level.

The required sample size observations to detect this size of r with 80% power is about 800 days. Therefore, findings of statistical non-significance of PM effect may reflect inadequate power to detect an effect of this magnitude if sample size is limited.

## 12.6.2 Sensitivity of Particulate Matter Effects to Model Specification in Individual Studies

### 12.6.2.1 Model Specification for Acute Mortality Studies

Many different statistical models have been used to interpret short-term mortality and morbidity studies. The model specifications and methods used to interpret the long-term studies are generally different from those used in analyzing the short-term studies. It is often difficult to compare estimates of PM effect in different studies when the estimates of effect size are obtained by different methods. Differences in effect size estimates may then occur because of differences in modelling approach as well as any real differences in response to PM exposure.

## TABLE 12-25. SAMPLE SIZE, SIGNIFICANCE, AND OTHER CHARACTERISTICS OF RECENT STUDIES ON DAILY PARTICULATE MATTER/MORTALITY IN U.S. CITIES

| Area | Period | Sample Size | t-ratio | Population | Daily Number Deaths | PM measure and mean[a] | Lag and Average | Reference |
|---|---|---|---|---|---|---|---|---|
| Birmingham, AL | 1985-1988 | 1,087 | 2.52 | 884,000 | 17 | PM10; 48 | same + 2 prev-day | Schwartz (1993a) |
| Cincinnati, OH | 1977-1982 | 2,191 | 3.47 | 873,224 | 21 | TSP; 76 | same-day | Schwartz (1994a) |
| Cook Co., IL | 1985-1990 | 1,357 | 3.43 | 5,300,000 | 117 | PM10; 38 | same-day | Ito et al. (1995) |
| Detroit, MI | 1973-1982 | 3,652 | 3.76 | 1,200,000 | 53 | TSP; 87 | prev. day | Schwartz (1991a) |
| Kingston, TN | 1985-1986 | 330 | 1.07 | 640,887 | 16 | PM10; 30 | prev. day | Dockery et al. (1992) |
| Los Angeles, CA | 1985-1990 | 364 | 1.96 | 8,300,000 | 153 | PM10; 58 | same-day | Kinney et al. (1995) |
| Santa Clara, CA | 1980-1986 | 549 | 2.86 | 1,400,000 | 18 | COH; 67 | same-day | Fairley (1990) |
| St. Louis, MO | 1985-1986 | 311 | 2.17 | 2,356,460 | 56 | PM10; 28 | prev. day | Dockery et al. (1992) |
| Steubenville, OH | 1974-1984 | 4,016 | 4.66 | 163,099 | 3 | TSP; 111 | prev. day | Schwartz and Dockery (1992b) |
| Philadelphia, PA | 1973-1980 | 2,726 | 5.04 | 1,688,710 | 48 | TSP; 77 | same+prev-day | Schwartz and Dockery (1992a) |
| Utah Valley, UT | 1985-1989 | 1,706 | 4.78 | 260,000 | 3 | PM10; 47 | same+4prev-day | Pope et al. (1992) |

[a]$\mu g/m^3$, unless otherwise noted
[b]12XCOH, unitless

Note: When multiple models were presented, the model with single pollutant (PM) and weather, season variables for the entire year was chosen.

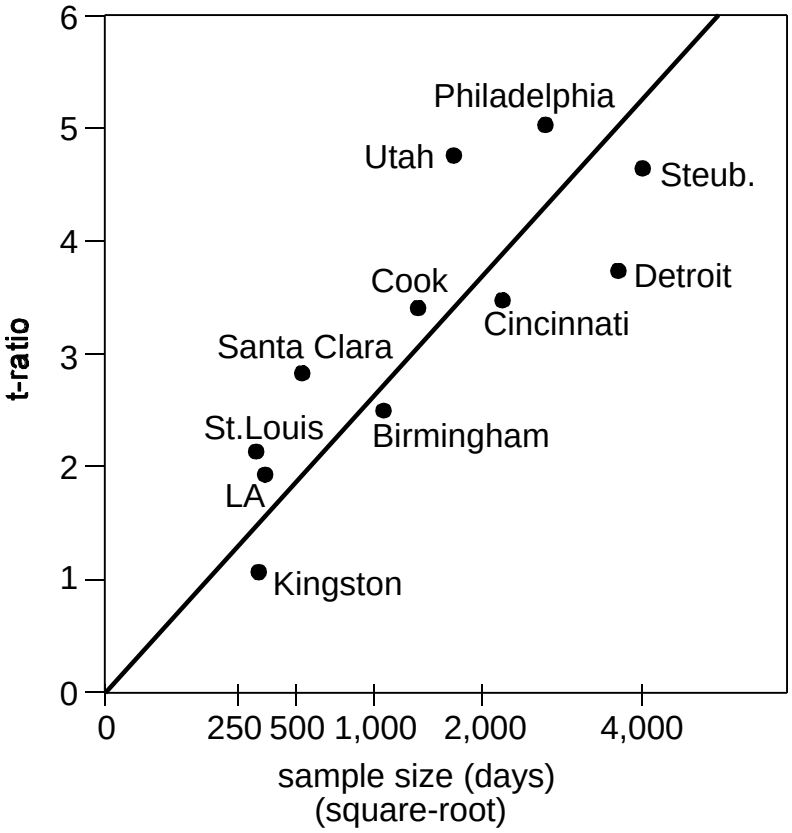


**Figure 12-17. t-Ratios of particulate matter coefficients versus sample size (days) from 11 recent U.S. studies.**

Many of the papers reviewed in this chapter provide enough information to assess the authors' choice of their "best" model, which we have reported in the summary tables. An extensive discussion of alternative modelling approaches for short-term exposure studies was already evident in earlier papers, such as the analyses of BS in London in the 1960's (Ostro, 1984; Thurston et al., 1989; Schwartz and Marcus, 1990; Ito, 1990), KM in Los Angeles (Shumway et al., 1988; Kinney and Ozkaynak, 1991), and COH in Santa Clara (Fairley, 1990). More recent work has moved in some substantially different directions, recognizing the non-Gaussian nature of discrete data such as daily death counts and hospital admissions, and incorporating a growing variety of data-driven non-parametric or semi-parametric models for PM and other covariates. The more recent studies are discussed below, emphasizing those studies in which $PM_{10}$ or TSP are used as PM indicators.